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THE TOXEMIAS OF PREGNANCY

MEDICINE MONOGRAPHS

VOLUME XV

THE TOXEMIAS OF PREGNANCY

BY

H. J. STANDER

Associate Professor of Obstetrics,
Johns Hopkins University
Medical School

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H. J. STANDER

The Johns Hopkins University and Hospital

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THE TOXEMIAS OF PREGNANCY

INTRODUCTION

By the term "Toxemias of Pregnancy" is usually understood a group of disorders associated with gestation, which account for about 26 per cent of the total maternal mortality incident to child-birth. To correctly classify, determine the etiology of, and successfully treat these disorders, has been, and still is, one of the most important problems in obstetrics. Fortunately, the incidence of these disturbances is relatively small, and pregnancy follows an uneventful course in the majority of cases. Normal gestation is always accompanied by marked alterations in metabolism, and because the toxemias of pregnancy may be intimately associated with these metabolic changes, it is necessary that the latter be given due consideration before one discusses the toxemias of pregnancy.

CHANGES DURING NORMAL PREGNANCY

We are still in the dark as to the exact nature of the stimulus which gives rise to the very marked anatomical and physiological changes occurring in the mother during gestation. From the investigations of of Kruieger and Offergeld it is fairly well established that the central nervous system has no influence on pregnancy and the only effect the sympathetic system may have is on the maternal circulation. Goltz and Ewald have removed the entire lumbar cord in bitches without disturbing the progress or even the onset of pregnancy. It is, therefore, quite probable that stimuli of a chemical nature are responsible for the changes attending normal pregnancy. One immediately thinks of the corpus luteum. Ash-Upmark reports the completion of a normal pregnancy 269 days after bilateral oöphorectomy had been performed. He furthermore collected several cases from the literature where complete castration had been effected during the first month of gestation without interruption of the pregnancy. We are as yet unable to state whether or not any hormone or hormones arising

from the corpus luteum or ovary are essential to the onset of pregnancy, although we are certain that in the human, at least, pregnancy may proceed from the first few weeks to a successful completion without the aid that may come from the ovary.

It is conceivable that the stimulus for the maternal changes may come from the foetus or from the placenta. Starling suggested that such a stimulating hormone may be in the tissues of the foetus. Halban believes that a placental hormone is responsible for the enlargement of the mammary gland. Cova has made extended experimental studies of placental secretions and states that alcoholic extracts of the placenta will produce hypertrophy of the uterus, vagina and mammae, and that such endocrine glands as the ovaries, adrenals and thyroid will undergo greater development as a result of the action of the internal secretion of the placenta. Guggisberg also regards the placenta as an organ of internal secretion. Abderhalden thinks there are specific ferments depending upon the placenta.

The exact nature of this stimulus has not yet been determined, although the weight of the evidence indicates that it is a chemical substance, probably a hormone, arising in the placenta or foetal tissues, which is responsible for the anatomical and physiological changes in the maternal organism.

1. Weight

As early as 1862, Gassner showed that there was a progressive increase in the weight of the mother greater than the increase in the weight of the foetus and the reproductive organs. This is undoubtedly due to an increase in other parts of the mother's body. Davis, who studied 150 cases, found that the average gain during pregnancy was 21 pounds and the average weight of babies, 6 pounds and 15 ounces. Zangemeister showed that the pregnant woman reaches her greatest weight the third day before the onset of labor, and that in the few days immediately preceding labor, there is a definite loss in weight. His results were in part corroborated by Hirsch who found that the greatest weight was reached on the sixth day before labor, and that from the sixth to the fourth day preceding labor, the weight remained stationary. He also observed a decrease in weight immediately preceding labor. Hirsch regards the hypophysis, which becomes active

at the beginning of labor, as responsible for this decrease in weight. Kemper on the other hand thinks that the loss of weight preceding labor and amounting to about 1 kgm. can be explained by an increase in excretory function of the mother as well as by a lessened food intake. Hannah believes that the gain in weight in the mother is greater in the primipara than in multipara.

Zangemeister has for a long time claimed that the loss of weight at the end of pregnancy is a sign of impending labor. Biehle, who has made a careful study of 40 selected healthy pregnant women, without any signs of toxemia, found such a decrease in weight in only 63 per cent of his cases, and does not agree with Zangemeister that the weight of the patient at the end of pregnancy is an index as to whether or not pregnancy should be terminated.

We may conclude that the maternal organism undergoes a progressive increase in weight, until shortly before labor, that this increase in weight is far greater than the increase in weight accounted for by the product of conception and the growing uterus with its adnexa, and that immediately before labor there is a reduction in the weight of the mother, amounting to about 1 kgm., but that this reduction in weight is not always a satisfactory index of impending labor.

2. Blood volume

It is the general opinion that the maternal blood volume increases steadily during pregnancy. Kaboth has estimated that the total increase in blood volume during gestation is about 400 cc. Gueissaz and Wanner, by injecting glucose and noting the refractive index of the serum, observed an increase in blood volume amounting to approximately 15 per cent. Miller, Keith, and Rowntree, using the vital red method, as well as Stander and Creadick, working with the carbon monoxide method on dogs, noted an increase in the maternal blood volume. Bohnen and Borrman by injecting congo-red intravenously found the average normal in healthy non-pregnant women to be 6.4 per cent, in the first half of pregnancy 7.63 per cent and at the tenth month 7.0 per cent. The dye methods measure the plasma, the carbon monoxide or cell method measures hemoglobin, consequently the total blood volume must be the sum of these two. Also the ratio of

plasma to cells is not constant; yet, bearing in mind these considerations the experimental work to date indicates that in the latter half of pregnancy there is a definite increase in blood volume.

While considering the blood volume it is advisable to know the behavior of the blood moisture. Pregnancy seems to be associated with a dilution of the blood. The specific gravity of the blood was investigated by Nasse, Lloyd-Jones, and Zangemeister, and these authors are agreed that a decrease in specific gravity takes place as pregnancy proceeds. From these observations as well as from the work on the distribution of serum proteins by Plass and others, it is fairly certain that pregnancy brings about an increased hydration of the blood. Stander and Tyler state that during gestation the water content of the blood is usually between 77 and 82 per cent, the accepted normal limits. Furthermore, when the blood moisture is determined month by month during pregnancy, characteristic fluctuations become apparent. It increases gradually, until the seventh month, and subsequently remains stationary, or slowly decreases. At the onset of labor it is approximately the same as at the beginning of pregnancy, and the act of labor has no constant influence upon the blood moisture. Plasma presents the same type of variation as that shown by the whole blood. Schmidt, Bickenbach and Jonen experimenting on dogs found the blood water content to increase during pregnancy. Gestation is undoubtedly accompanied by an hydration of the blood and a true increase in blood volume, which is perhaps associated with a decrease in red cell count and hemoglobin percentage.

3. Protein metabolism

There are many investigations on protein metabolism during pregnancy. The pregnant woman undoubtedly absorbs protein as well as the non-pregnant, as shown by the observations of Hoffström in a primipara during the last months of pregnancy. Pregnancy represents a gain in nitrogen in the mother.

Experiments of Hoffström showed that there was a very definite positive nitrogen balance during the second half of pregnancy. He carefully studied the nitrogen intake and output from the sixteenth week until the end of pregnancy, and found that the mother completed

the pregnancy with a net gain of 209 grams of nitrogen. Wilson followed the nitrogen balance in three normal pregnancies, and came to the conclusion that in normal pregnant women, a storage of nitrogen begins at a very early period, and that the amount of nitrogen stored is greatly in excess of the actual needs of the developing ovum. It is fairly well established from the work of these investigators, as well as of Mahnert, Bar, and Landsberg that there is a positive nitrogen balance during pregnancy and particularly during its second half.

Eufinger examined the various protein fractions of the blood during pregnancy and found that they underwent a change or shifting. His findings show a relative decrease in total proteins, and a progressive increase in fibrinogen, globulin and euglobulin, but a marked decrease in albumin; and in 350 women during pregnancy there was a marked decrease in the stability of the plasma colloids, as tested by the Gerloczy reaction.

Plass and his co-workers have also made a study of the different protein fractions in the blood plasma of normal pregnant women. These investigators found that beginning with the third month of gestation, there is a gradual diminution of plasma protein, and that this decrease reaches its maximum at the fifth month. During the last few months of pregnancy, the dilution tends to be less marked, and there is a further concentration at the time of labor. They further observed that the relative plasma volume as measured by hematocrit readings, follows inversely the plasma protein concentration, and therefore, they regard the decrease of the plasma protein as a result of true dilution. Plass concludes that the plasma proteins tend to decrease during pregnancy and the early part of the puerperium; that the serum albumin is decreased to such an extent that the drop in the total proteins can be explained by the concentration of this fraction; and that fibrinogen increases during pregnancy while the serum globulin shows only a slight relative increase, the absolute values remaining constant. Kraul also demonstrated that the fibrinogen content of the blood increases during pregnancy, rises still more during labor, and slowly returns to its normal level during the puerperium. This author believes that increased fibrinogen plays some part in the production of thrombosis following delivery. This increase in fibrinogen in the human being during gestation is further proven by the work of Muller and Dienst. Schmidt,

Bickenbach and Jonen investigated the fibrinogen content of the blood in dogs, and found that pregnancy was associated with a very definite increase of fibrinogen content of both whole blood and plasma.

At present there is some controversy concerning the amino acids of the blood during pregnancy. The amino acids are composed of very definite fractions, which, according to Hellmuth, may be grouped as (1) alphatic mono-amino-acids (glycocoll); (2) alphatic di-amino-acids (lysin, arginin); (3) aromatic and heterocyclic amino-acids with and without primary amino-N (histidin and prolin). Hellmuth is of the opinion that there is no marked change in any of these during pregnancy. Schlossman is also convinced that pregnancy is not associated with a change in amino-acid content of the blood. Runge and Juhl found that in normal pregnancy there was 32 mgm. per cent of amino acid in the blood, as compared with 27.3 mgm. in normal non-pregnant women. Frey, on the other hand, found a very marked increase in amino acids during pregnancy. From a careful study of all the results reported in the literature it seems safe to conclude that there is no marked change in the amino acids during gestation.

We have seen what profound alterations in protein metabolism accompany gestation and it is thus reasonable to expect differences in the excretion of nitrogen in the maternal organism. As early as 1894 Zachrjewski showed a decreased excretion of nitrogen in the urine during pregnancy. According to the investigations of Hasselbach, the woman in the latter half of pregnancy excretes 9.2 grams nitrogen every day, whereas immediately after birth her daily output of nitrogen rises to 11.4 mgm. Mahnert, in an attempt to determine whether or not the increase in weight during pregnancy is due to a sparing of nitrogen, studied the total metabolism in pregnant women from the fourth to the tenth month. He came to the conclusion that there was a definite increase in the protein metabolism, and is of the opinion that the increase in body weight can be explained on this basis. He furthermore believes that the terminal loss in weight, discussed above, is due to an increase in protein metabolism, although he was unable to determine the cause or causes of such an increase in protein metabolism immediately preceding labor.

Bock finds that the C:N ratio is increased during pregnancy (*C* is the elementary organic carbon, and *N* the nitrogen, in the urine).

This C:N ratio in the urine is supposed to be an index of the degree of oxidation of intermediary metabolism products. An increased excretion of *C* denotes a decrease in the oxidative processes of the intermediate metabolism. Bock concludes that in normal non-pregnant persons the ratio C:N is 0.85 (Bickel); that in pregnancy this ratio increases to 1.13; and that this increase in C:N ratio is due to an increase in carbon as well as to a decrease in the nitrogen excretion.

Murlin studied the distribution of the nitrogen fractions of the urine in three cases of normal pregnancy. Both Bar and Murlin showed that there is a diminished excretion of urea in the urine during pregnancy and an alteration in the nitrogen distribution in the urine, because while the amount of urea excreted is diminished the quantity of ammonia or the so-called "ammonia coefficient" is increased. Wilson showed that the amino acid nitrogen in the urine is increased, and Falk and Husky have demonstrated polypeptide nitrogen in the urine of pregnant women. It is of interest to note that creatine appears in the urine during the latter part of pregnancy, as first shown by Krause and Cramer and amply confirmed by later investigations.

After having studied the positive nitrogen balance during the latter half of gestation, the changes in the protein fractions of the blood and the altered nitrogen partition in the urine accompanying pregnancy, it is essential that we inquire into the non-coagulable or non-protein nitrogen of the blood. As the result of the findings of a large number of workers (Folin, de Wesselow, Williams, Hellmuth, Plass, Stander, King and Denis, Harding, Allin and Van Wyck, Bunker and Mundell, and Jung), we are able to state that the non-protein nitrogen content of the blood during pregnancy is the same as, or very slightly less than, in the normal non-pregnant woman, in the neighborhood of 30 mgm. per 100 cc. blood. Caldwell and Lyle found a slightly higher value in a series of 150 analyses on pregnant women.

In the normal non-pregnant woman the blood urea nitrogen forms approximately 50 per cent of the total non-protein nitrogen. Killian and Sherwin, Caldwell and Lyle, Williams, De Wesselow, Folin and Stander have found a lowering of this ratio during pregnancy. Dilution of the blood, decreased production of urea and an increase in the undetermined or rest-nitrogen are among the theories which may explain this lowering of urea-nitrogen to non-protein nitrogen ratio in the blood of the maternal organism.

Normal pregnancy is not associated with any marked changes in creatinine, creatine or uric acid in the blood, although it must be admitted that our method for determining creatine is still open to criticism.

4. Fat metabolism

Normal pregnancy is associated with a marked alteration in the concentration of the blood lipoids. During the latter part of pregnancy, fat, lecithin and cholesterol show a marked increase. Slemons and Stander found that at term there are approximately 900 mgm. of fat per 100 cc. of maternal blood, while the blood of the normal non-pregnant woman contains about 600 cc. of fat per 100 cc. These authors regard the increase in fat, lecithin, and cholesterol as a preliminary step in the preparation for lactation. Tyler and Underhill have corroborated these findings and conclude that the total neutral fat of whole blood in pregnant women becomes higher than the non-pregnant values as early as the third month of pregnancy, and that there is a progressive increase from then till term. They also found that cholesterol, cholesterol-esters and lecithin increase gradually until term, when each is roughly one-third higher than at the third month. Hellmuth, Hermann, Neumann and Lindemann and Chauffard-Grigaut come to the same conclusion, namely, that there is an increase in neutral fat as well as in lipoids during pregnancy.

5. Carbohydrate metabolism

It is well known that pregnancy is often accompanied by a glycosuria, although the amount of glucose in the blood may not be increased. The work of Kämpf, Bergsma, Benthin, Morris, Stander and Radelet, Hellmuth, and Novak and Bermann shows that the blood sugar during pregnancy is not elevated, and some of these authors even found values slightly below normal. The so-called pregnancy glycosuria is probably due to a lowering of the renal threshold for glucose (Nürnberger, Gottschalk), or it may be connected with excessive activity of the pituitary gland, as suggested by Wallis and Bose. After Schirokauer had examined the blood sugar in cases of pregnancy glycosuria, Grunthal experimented on many such patients and stated that the sugar tolerance figure in pregnancy is the same as in the normal

pregnant woman. This author came to the conclusion that the pregnancy glycosuria does not depend on the sugar level in the blood. During labor and often shortly before labor the sugar in the blood increases according to Walthard. Many pregnant women when subjected to a blood sugar tolerance test show glycosuria and this fact has been utilized by Frank and Nothmann to furnish a test for the existence of pregnancy. Bokelmann and Rother have given an excellent review of this subject and have also themselves tried the sugar tolerance test for pregnancy in 48 women. They came to the conclusion that the test is not of great value and that more reliance could be placed upon a clinical examination of the patient.

In considering the carbohydrate metabolism it is well that we bear in mind its relation with fat metabolism. It seems fairly well established that the usual relationship of carbohydrate to fat is disturbed during pregnancy. Acetone bodies (di-acetic and B-oxybutyric acids) are regarded as the intermediate oxidation products of the fatty acids, and their excretion in the urine is greatly increased when carbohydrates are witheld from the diet. Vicarelli in 1893 noted the presence of acetone bodies in the urine of pregnant women. A diet poor in carbohydrates (Porges and Novak, Harding) leads to an excretion of acetone bodies in the urine in a normal pregnant woman, while a non-pregnant woman on an identical diet will show no acetone in her urine. Bokelmann and Bock observed 39.48 mgm. acetone bodies per 100 cc. blood in normal pregnancy as compared with 29.85 in the non-pregnant woman. This increase in acetones in the blood they believe to be due to a deficient supply of carbohydrates, to an abnormal metabolism of carbohydrates or to a primary change in fat metabolism.

In addition to this increase of acetone bodies in the blood and the tendency towards acetonuria associated with pregnancy, there is also an increase in blood lactic acid, according to Bokelmann and Schultze. Lactic acid arises from carbohydrate and is formed during the contractile phase of muscular contraction. Most of the lactic acid formed is resynthesized to glycogen. Bokelmann believes that the lactic acid increase in pregnancy is a result of a slowing down in carbohydrate metabolism, a disturbance in oxidation of lactic acid to carbonic acid and water, or a retardation in the resynthesis of lactic acid to glycogen. Kielin, Zweifel, and Stander and Radelet were

unable to notice any marked changes in blood lactic acid during normal gestation.

6. Acid-base equilibrium

The alveolar CO_2 tension is lowered during pregnancy as first shown by Hasselbalch. This lowering of the CO_2 tension probably manifests itself as early as the second month of gestation according to very painstaking work of Hasselbalch and Gammeltoft. These investigators found the alveolar CO_2 tension during the latter stages of pregnancy to be from 30 to 35 mm. Hg, limits agreeing well with the observations of Rowe. The CO_2 combining power of the blood is also definitely decreased. Losee and Van Slyke, Cook and Osman, Slemons, Emge, Stander, Williamson, Bokelmann, Schmidt and Wingen, and others have noted a marked drop in the CO_2-combining power of the blood as pregnancy approaches term. Some authors believe this so-called "acidosis of pregnancy" to be dependent on the acetone bodies and lactic acid in the blood, as referred to above. As we shall see later, pregnancy means a great carbohydrate drain for the mother and Schmidt and Wingen believe that this increased carbohydrate requirement in pregnancy is met partly by fat being converted in the liver into glycogen, and that during this transformation acid by-products may appear and these use up some of the alkali reserve of the blood. This lowers the capacity of the blood for combining with CO_2, resulting in a lowered alveolar CO_2 tension.

This acidosis of pregnancy is probably a compensated one. Hasselbalch and Gammeltoft examined the hydrogen-ion concentration of the serum and found it to be slightly changed at the end of pregnancy. Bock gives the pH for normal people as 7.52, in the early months of gestation as 7.51 and at the end of pregnancy 7.47. After labor the pH returns to its normal value of 7.52. This author concludes that it is only during the last weeks of pregnancy that the actual reaction of the blood is changed, and that this slight change is brought about by the buffer capacity of the blood. We may conclude that pregnancy is associated with a relative acidosis, but that any change in the acutal reaction of the blood must be very slight.

7. Basal metabolism

There is little doubt that pregnancy is associated with an increase of the total metabolism of the mother. Magnus-Levy noted that the oxygen absorption in the eighth month of pregnancy was 17 per cent higher than at the third month. In the normal woman at term the basal metabolic rate is about 4 per cent higher than in the normal non-pregnant woman in complete sexual rest (Zuntz, Hasselbalch, Carpenter and Murlin). These authors found that the heat production per unit of weight for the puerperal woman was 11 per cent higher than for the normal non-pregnant, and 7 per cent higher than for the same woman at term.

In 1921 Baer reported the basal metabolic rate in 44 normal pregnancies. He observed that during the latter part of pregnancy, this rate averaged more than 30 per cent above the normal non-pregnant woman. Two years later Cornell investigated the basal metabolism in 84 pregnant women. He also found an increase in the basal rate. This increase in basal metabolism during pregnancy has been confirmed by Sandiford-Wheeler, Root-Root, Rowe, Alcott, Waldemier, and Stander and Peckham. The increased basal rate is probably dependent upon the growing product of conception, as well as upon an increased activity of the thyroid gland. Pregnancy probably does not result in any marked alterations in the energy exchange, beyond that produced by the growth of the foetus.

8. Mineral exchange

According to the work of Camerer and Soldner on the ash of the human foetus, there is a preponderance of calcium and phosphorus in the foetus, and these two substances are present in higher concentration in the foetal than in the maternal blood according to v. Oettinger. There must be a considerable drain on the mother as far as these two elements are concerned. According to the last author there is 10.2 mgm. per cent of calcium in the normal non-pregnant woman, whereas the figure for normal pregnancy is 9.8 per cent. His figures for inorganic phosphorus are 3.6 mgm. for non-pregnant individuals, and 3.3 for normal pregnancy. A slight decrease in calcium in the maternal blood has also been noted by Bock, Plass and Bogert, Ivanyi,

Rodecurt, Linzenmeier, Dibobes, Kvater, Schonig, Krebs and Briggs, Hetenyi, Liebmann, and Stander, Duncan and Sisson. A few authors (Serdjukoff, Morosova and others) observed no change in the calcium content of the blood during pregnancy, but the weight of evidence points to a slight lowering of the blood calcium, as the woman approaches term. The inorganic phosphorus is probably not much altered during gestation. De Wesselow and v. Oettinger noted a slight decrease, while Rodecurt observed a slight increase, and Bock and Stander could find no difference between the non-pregnant and pregnant values for inorganic phosphorus.

There is very slight difference in sodium in the pregnant and non-pregnant, v. Oettinger giving an average figure of 329.4 mgm. per cent for the non-pregnant woman. Harding, in his review on the metabolism of pregnancy, collected figures from various authors and believes that these show that sodium decreases slightly in concentration in the serum while there is an increase in the corpuscles, and that this also holds true for calcium and chlorine. Stander and his co-workers could find no marked change in sodium during pregnancy. The values for potassium and magnesium are also about the same for pregnant as for non-pregnant women.

The foetus must derive its iron from the maternal organism, and it gets a large part from the mother's hemoglobin. The foetus requires iron for building its own hemoglobin and for its nucleo-proteins. In the adult, nucleo-protein is probably the best source for iron required in the manufacture of hemoglobin, and it is possible that the foetus may get part of its iron from a food nucleo-protein or an organized nucleo-protein in the mother's blood. Williams feels convinced that the foetus takes up iron directly by means of the syncytium from degenerated maternal red blood cells. Charrin believes that the reserve iron of the mother is stored in the spleen and is reduced during gestation. It is interesting to know that much more iron is stored in the liver of the young rabbit at birth, than in an adult rabbit. This is probably true for the human foetus as well.

9. Hormones

The thyroid gland undoubtedly undergoes a change during pregnancy, becoming more vascular and showing a definite hypertrophy.

Davis, in a study of 520 women, found visible signs of thyroid hypertrophy in 41 per cent during early pregnancy. The enlargement is a true hyperplasia. The significance of hypertrophy of the thyroid gland is not yet clear. Halsted found that in pregnant dogs from which the thyroid gland was removed, the puppies showed a tremendous enlargement of the thyroid, indicating that there was a compensatory hypertrophy because of the lacking secretion in the mother. Seitz states that there is also an increase in colloids of the thyroid. The para-thyroid gland likewise undergoes a marked change during pregnancy. The chromophile cells multiply in number and are better outlined, from which one may deduce that their function is increased during pregnancy. We know that the para-thyroids are intimately associated with calcium metabolism and it is possible that the changes noted above in calcium are dependent upon the changes in the para-thyroid. We are unable to say whether the pancreas undergoes any morphological changes during gestation; although there is very little doubt that the carbohydrate metabolism is altered. The ovaries present differences during pregnancy. The corpus luteum of pregnancy is a well known entity, but, as stated earlier in this paper, pregnancy can proceed to a successful completion, even after the removal of both ovaries as early as the first month of pregnancy. On the other hand, the most characteristic change in the ovaries of pregnant women consists in atresia of the follicles, which is characterized by development up to certain stage without rupture, but with such hyperplasia of the connective tissue cells of the inner layer of the theca, as to suggest that they must have some internal secretory activity. These changes are so pronounced that any one familiar with the histology of the ovaries can readily differentiate between those derived from pregnant and those from non-pregnant women. There is little doubt that the adrenals present a marked hypertrophy of the cortex during gestation. Whether this means an increase in adrenalin in the body is not known. Some authors have tried to link up the change in carbohydrate metabolism with increased production of adrenalin. In 1904 Launois and Mulin showed that pregnancy was always associated with a hypertrophy of the hypophysis. It is the anterior lobe of this gland which undergoes regular hypertrophy, but the significance of this is far from clear. The posterior lobe of the gland does not

hypertrophy, although it is well established that it is this part of the pituitary which is connected with the stimulating effect on the uterine contractions. The placenta is regarded by many as an important organ of internal secretion. De Lee states that placental hormones stimulate the development of the uterus and probably activate the thyroid, para-thyroid, pituitary and adrenal gland. Some writers are of the opinion that the placenta when fully developed takes over the functions of the ovary and corpus luteum.

10. Neuro-vascular system

According to Freund 50 per cent of all pregnant women show dermatographism, and according to Hinselmann and Nevermann and others, 60 per cent of all pregnant women show capillary spasm. It would therefore appear that pregnancy is associated with changes in the sympathetic, and para-sympathetic systems. There are also certain blood diseases peculiar to pregnancy. Chlorosis, which was formerly so common among young girls, is said by some authors to develop during pregnancy. The total number of blood cells is decreased, although during the latter part of pregnancy there is a definite increase in the blood corpuscles. We are also acquainted with a pregnancy anemia which simulates pernicious anemia, but instead of terminating fatally it often eventuates in spontaneous recovery after the completion of the puerperium. This is supposed to be due to the destructive action exerted upon the maternal red cells by the chorionic epithelium. Pregnancy hemolysis, pregnancy hemoglobinemia and pregnancy hemoglobinuria also occur. Most authors believe this hemorrhagic diathesis to be due probably to a change in the endothelial covering of the capillary vessels. The white blood cells usually show a leucocytosis during normal gestation. The skin is often affected by gravidity. The pigmentation of the nipples and areola is is very common. Cloasma, or pigmentation of the face, occurs less frequently.

11. Heart output

As early as 1827 Larcher stated that pregnancy was always accompanied by a marked cardiac hypertrophy. Dreysel found that the heart of a pregnant woman invariably weighed more than that of a

normal non-pregnant individual. It has often been stated that true hypertrophy of the heart occurring during pregnancy, is caused by the placental circulation, compression of the aorta by the uterus, or by the increased circulation in and around the uterus. It has also been suggested that an increase in the output of the heart is caused by the increased peripheral resistance brought about by some vaso-constrictor substance circulating in the blood stream. Lockhead and Cramer examined extract of the placenta, and found that this contained no vaso-constrictor substance. There is no, or only a slight, increase in the blood pressure during normal pregnancy. Slemons and Goldsborough however, demonstrated a considerable increase in pulse pressure which was especially marked during the later months of pregnancy. Jaschke came to similar conclusions. The "cardiac output" measured directly in the dog, by Stander, Duncan and Sisson, revealed that during pregnancy the minute volume is markedly increased, being one-third to one-half greater than in the non-pregnant animal. Whether this increased output is the result of hypertrophy of the heart or not, has not yet been determined, but it seems probable that it is at least in part accomplished by drawing upon the reserve force of the heart. Frey, however, is convinced that actual cardiac hypertrophy does occur during normal gestation.

CLASSIFICATION OF THE TOXEMIAS OF PREGNANCY

We have seen what profound anatomic and metabolic changes take place in the maternal organism during normal gestation. Many of these alterations become more marked in the presence of a toxemia, and it has been the object of numerous clinical and experimental investigations by a vast number of workers to determine whether and, if so, in what manner, these various departures from the normal may be specifically linked up with the etiology and course of the different toxemic disorders. There has been one universal drawback in all this work, which is particularly evident when one attempts to correlate the ultimate findings of different investigators. This drawback has been, and still is, the lack of a uniform method of classifying the various types of toxemia of pregnancy. Different clinics are wont to use different classifications, a practice which has only served to confuse those who attempt to compare the work and results of these

different clinics. It is, of course, apparent that the real cause of such discordance is our profound ignorance concerning the etiology of the disorders which we are endeavoring to classify and study. As Kellogg of Boston very aptly puts it, "The conquest of the toxemia of pregnancy depends primarily on a universal acceptance in this country of some index, of some classification, some coöperative mode of study in every great obstetric center," and he very wisely suggests that a committee of representatives of the obstetrical societies meet with a view to establishing a working index or classification, tentative at first and changeable at each yearly meeting.

The main difficulty arises when an attempt is made to classify the so-called "pre-eclamptic" and "nephritic" toxemias which may complicate pregnancy. Vomiting of pregnancy, acute yellow atrophy of the liver, and eclampsia are well defined entities and usually recognizable. All agree that nephritis may complicate pregnancy, but it is sometimes rather difficult to recognize and classify the various types of kidney lesions during pregnancy and to make a differential diagnosis between the nephritic and pre-eclamptic toxemias. Indeed, it is often impossible to know with which condition we are dealing until the patient has reached the end of the puerperium, or has come to autopsy.

Williams in the last edition of his text-book classified the toxemias of pregnancy as follows: (*a*) pernicious vomiting (*b*) acute yellow atrophy of the liver (*c*) nephritic toxemia (*d*) pre-eclamptic toxemia (*e*) eclampsia and (*f*) presumable toxemias. DeLee groups them as follows: hyperemesis, ptyalism, gingivitis, eclampsia and allied conditions, kidney of pregnancy and acute yellow atrophy of the liver. Under eclampsia and allied conditions he discusses eclampsia, eclampsia reflectorica, acute toxemia (eclampsia without convulsions) and nephritic eclampsia. Zangemeister in his recent book gives the following classification:—hyperemesis, hydrops, nephropathia and eclampsia. In the present discussion, the author is not considering such complications as chorea, skin affections, anemia, hemophilia, neuritis or psychoses.

There is a mild type of toxemia manifesting itself usually in the eighth or ninth month of pregnancy, and consisting of a slight elevation of blood pressure, a slight amount of albumin in the urine and moderate swelling of the ankles. As soon as the patient has been delivered the symptoms disappear completely, and in a subsequent pregnancy

the condition may recur or may be absent. Kellogg speaks of this as recurrent toxemia of pregnancy, and states that such a recurrence should be considered as a chronic entity distinct from the common kidney disease complicating pregnancy. Moreover, he is of the opinion that it may be subdivided into two groups: (1) in which under the strictest possible prenatal care the prognosis for both mother and child is good and (2) in which the prognosis for the child is bad, no matter what the prenatal care may be. Von Geldern studied the subsequent history of 27 women with toxemia of pregnancy, and found that 13 of them had one or more normal pregnancies following the toxemia; while 14 had a recurrence. He states that in cases of "recurrent toxemia" without permanent damage to the kidney, the prognosis is difficult. Stander and Peckham (1926) made a study of the toxemias in repeated pregnancies in the same individual and came to the conclusion that there is a group, which they designate as low reserve kidney, in which it is impossible to demonstrate any signs, symptoms or laboratory findings suggesting nephritis. It seems to the author that many of the "recurrent toxemias" belong in this category, as well as the simple "albuminuria of pregnancy."

Mussey has attempted to group the nephropathies of pregnancy, and has directed our attention to the classification of Volhard and Fahr, which is as follows:

A. Pyelitis and pyelonephritis.
B. Hypertension and nephritis.
    1. Acute nephritis
        a. Acute glomerulonephritis.
        b. Acute nephrosis.
    2. Chronic nephritis.
        a. Chronic diffuse glomerulonephritis.
        b. Chronic nephrosis.
    3. Sclerosis (vascular lesion)
        a. Benign hypertension.
        b. Malignant hypertension.

Mussey and Keith believe that the classification of nephritis during pregnancy into acute and chronic aids in establishing the prognosis. Patients with acute nephritis very rarely give a history of previous

kidney trouble. They state that in the acute type of nephritis, the presence of albumin in the urine, and the sudden rise in blood pressure with increased oedema, usually occur during the 8th or 9th month of gravidity, and that a kidney function test shows satisfactory excretion, with a urine of high specific gravity. On the other hand, patients with chronic nephritis often give a history of previous kidney trouble, and the hypertension, oedema and albuminuria make their appearance early in pregnancy, usually before the seventh month. In the latter, tests for renal function show poor excretion, with the specific gravity of the urine either fixed or low. These authors believe that it is possible to differentiate between the various types of nephritis during pregnancy. The subdivision of parenchymatous nephritis into acute glomerulonephritis and acute nephrosis is of quite recent origin. In acute glomerulonephritis there is albuminuria, oedema, hypertension and hematuria, the urine output is lowered and there may be eye ground changes. In acute nephrosis, on the other hand, the blood pressure is essentially normal, there is marked oedema, albuminuria and lowered output of urine, but no nitrogenous retention in the blood nor any eye changes.

Mussey divides the toxemias of the later months of pregnancy into three groups: (1) acute toxemias of the eclamptic type; (2) toxemias due to exacerbations of chronic nephritis; and (3) toxemias due to definite renal infection (focal nephritis and pyelonephritis). He further subdivides the acute toxemias of the eclamptic type into (a) those in which there is unquestionably pathologic evidence of disease of the liver and (b) those in which the symptoms of renal involvement predominate.

Von Jaschke regards the "kidney of pregnancy," first described by Leyden, as a non-inflammatory process. He advocates that all affections of the kidney, which are of a degenerative nature but not inflammatory, should be designated as "nephrosis," in which there is degeneration of the tubules, but no demonstrable changes in the glomeruli or vessels. He also adheres to Volhard's classification of the nephropathies into focal nephritis (infection), true nephrosis, sclerosis, and diffuse glomerulonephritis. In the nephrosis of pregnancy the excretion of water is delayed according to Von Jaschke; although the urine concentration tests show no impairment. This means that

there is a disturbance in water secretion outside of the kidney, and is due to inability of the water to reach the kidney, because of an abnormal permeability of the vessels. He also thinks that a toxin, which acts on the endothelium of the vessel walls, causes epithelial degeneration which results in the increased permeability.

Both Von Jaschke and Volhard are of the opinion that in addition to this degenerative process, with oedema but without hypertension, known as nephrosis, there also occurs a form which is liable to lead to eclampsia, and which presents the picture of typical diffuse glomerulonephritis. In the latter type of kidney disease there is hypertension and marked oedema. Baer thinks that the "kidney of pregnancy" occupies a place between nephritis and nephrosis and that the initial changes probably occur in the renal-vascular system. This author used functional tests in order to differentiate between the various types of renal disease. One of them consists in determining the changes in the specific gravity in a series of two hourly specimens of urine, with the object of ascertaining the functional activity of the tubular system. Another test is aimed at evaluation of the functional activity of the glomerular system. In a normal person an extra litre of water taken at any one time, will be excreted in less than four hours; while in nephritis there is definite delay in excretion. Baer concludes that nephrosis and nephritis are separate entities, involving different portions of the kidney tissue, and that it is possible by means of the two tests just mentioned, aided by capillaroscopy, urinalysis and blood pressure readings to differentiate between nephrosis and nephritis complicating pregnancy, and he believes that the prognosis is better in the former than in the latter.

Heynemann also differentiates between nephrosis and nephritis during pregnancy, and states that the histology of the eclamptic kidney is that of nephrosis (degeneration of tubules and glomeruli) and not a nephritis or an inflammatory process. He thinks that the nephrosis of pregnancy is really a glomerulonephrosis, and that healing in such conditions is quick and complete, and that such patients may go through subsequent pregnancies without further trouble. This author regards it a simple matter to differentiate between eclampsia and uremia complicating pregnancy, although there are no sure differential signs. A marked increase in blood pressure, the appearance of

erythrocytes in the urine and an albuminuric retinitis appearing in the second half of pregnancy are indicative of nephritis; and should the same signs appear in the first months of pregnancy, the condition must be considered as chronic nephritis.

At the present time, while our knowledge of nephritis complicating pregnancy is still quite meagre, it appears to the author that the use of the term "nephrosis," in classifying the toxemias of pregnancy, serves no useful purpose. By it is understood a mild degenerative tubular process, and it seems doubtful whether we are as yet able to diagnosticate a "nephrosis" during pregnancy. In our estimation, the term merely serves to cloak our ignorance and to obscure still further our knowledge.

In this paper the following classification will be used:

1. Vomiting of pregnancy
2. Low reserve kidney.
3. Nephritis complicating pregnancy
4. Pre-eclampsia
5. Eclampsia
6. Acute yellow atrophy of the liver

Low reserve kidney is probably identical with "kidney of pregnancy," with certain types of "recurrent pregnancy toxemia," with the simple "albuminuria of pregnancy" as well as with certain of the "nephroses" of pregnancy. The author is of the opinion that it is frequently impossible, especially when the patients' previous history is unknown, to differentiate between the various types of kidney diseases during the course of pregnancy, such as the acute and chronic nephritides and nephroses; and he is fully aware that the above classification, which he has suggested and will follow in all subsequent discussions, is tentative and perhaps inadequate, awaiting the discovery of the etiology of certain of these toxemias of pregnancy. This classification has been followed at the Johns Hopkins Hospital for the past three years and has proved fairly satisfactory, as less than five per cent of the patients suffering from a toxemia of pregnancy were placed in an "unclassified" group.

I. Vomiting of pregnancy

Vomiting occurs in approximately 50 per cent of all pregnancies, appearing at about the fifth or sixth week and lasting from six weeks to two months. Fortunately, in the majority of cases the vomiting is slight and we may speak of it as "morning sickness." According to Pick, vomiting of pregnancy may proceed to the pernicious stage in about one in every 1000 pregnancies. Williams is of the opinion that pernicious vomiting occurs more frequently, and that it is encountered once in 700 pregnancies among women of the upper classes in this country. It seems to be the general opinion that pernicious vomiting of pregnancy is more prevalent in the United States and France than in Germany and England.

It is generally stated that Soranus, in the latter part of the first century, was the first to describe the disease, but it was not until the nineteenth century that its importance was fully appreciated. In 1879 Matthews Duncan pointed out that pernicious vomiting is sometimes associated with definite liver lesions; and Williams, Ewing and Stone have directed attention to what they consider a characteristic type of liver lesion in severe cases of pernicious vomiting. Necrosis takes place in the central portion of the liver lobule, quite contrary to the usual findings in eclampsia. Instead of hepatic necrosis, marked fatty degeneration of the liver lobules may make its appearance. It is questionable if we are justified in speaking of a typical liver lesion of vomiting, because in the cases, that have been studied in the post mortem room, there have been superimposed the effects of marked starvation and dehydration, which in themselves produce typical histological changes. Because of the nature of the disease, we shall undoubtedly have to resort to animal experimentation to formulate a true concept of the pathological findings associated with vomiting of pregnancy.

It has been the custom to regard vomiting of pregnancy as of three separate and distinct types; (1) reflex vomiting (2) neurotic vomiting and (3) toxemic vomiting. Williams states that the neurotic is the most, and the reflex the least frequent type, and that toxemic is the most serious. Not all writers agree with this classification, some believing that vomiting of pregnancy is always due to neurosis, while others hold to a toxemic basis in every instance. After a discussion

of the work on the etiology of the disease, we shall return to the question of classification.

Etiology. There have been numerous theories concerning the etiology of vomiting of pregnancy. Tweedy believes that absorption of food particles during the early stages of their digestion is responsible for hyperemesis and that in early pregnancy a foreign element appears in the blood, and the normal food anti-bodies are thereby interfered with. Tweedy considers the vomiting of early pregnancy as Nature's effort to reject food incapable of proper neutralization. Siegert, on the other hand, believes in hunger as the cause of vomiting.

Levy-Solal attempted to discover whether women, suffering from vomiting of pregnancy, are sensitive to placental extract, and found that in the placenta of a vomiting patient there is an antigen which is reactivated by human serum and which produces shock in guinea pigs; this antigen is not present in young normal placentae, and at the end of pregnancy the placenta is also without such an antigen. He came to the conclusion that women with vomiting of pregnancy are sensitive to placental extract, and that after abortion they remain sensitive two to three days. After the fourth month of pregnancy these patients are no longer sensitive to such an extract. On the assumption that a toxin produced by the foetus or placenta is the cause of vomiting of pregnancy, Mack suggested the use of serum from normal cases of advanced pregnancy in the treatment of these patients, believing that the normal cases must have become immune to these toxins.

Hirst argues that every woman during her menstrual life is constantly absorbing corpus luteum substance, but that with the onset of pregnancy this absorption ceases. The corpus luteum of pregnancy increases in size until it reaches its maximum in the third month of gestation, and from this time on it is gradually absorbed. He calls attention to the fact that the vomiting of pregnancy disappears at about the time that the corpus luteum begins to decrease in size, and suggests that this is not a mere coincidence but that the corpus luteum plays an important part in relation to vomiting. With this idea in mind he has developed a treatment for vomiting of pregnancy which consists in administering corpus luteum extract.

Some authors believe that the neurotic element plays an important part in hyperemesis. Both Schwab and Lynch are of the opinion

that most cases of the vomiting of pregnancy can be explained on the basis of an underlying neurosis. Brindeau is also a firm adherent of the hysteria theory for the etiology of vomiting.

Heinrichsdorff, as a result of his studies in a large series of cases, regards hyperemesis as a typical disease of the first half of pregnancy in which it is often impossible to determine any organic disease. In many cases death may ensue and a post mortem reveal nothing positive. This author feels that hyperemesis is not derived from an intoxication, but that it becomes transformed into such. Kotz finds an over irritability of the vagus an underlying factor in most cases of vomiting, while Seitz thinks that it is due to reflex, psychic and toxic vagal-stimulation, and that the vagal changes may be caused by disturbances of inner secretion.

Ferru is of the opinion that hepatic insufficiency in severe cases of vomiting of pregnancy is not the pathological cause, nor is it of great prognostic value, as is usually believed. It is the consequence and not the cause of vomiting according to this author. Sella regards insufficient ovarian activity as the cause, while Silvestri, Rebaudi, Sergent and Rathey think that in insufficient adrenal and poly-grandular activity one may discover the cause of vomiting of pregnancy.

In 1919 Harding and Duncan advanced the theory of glycogen deficiency in the liver of the mother as the cause of vomiting of pregnancy. They came to this conclusion because most patients suffering from vomiting of pregnancy showed ketonuria, and because these patients improved on a diet rich in carbohydrates. Since the appearance of the paper of these two authors a great deal has been written about carbohydrate deficiency in vomiting of pregnancy. Titus believes that the carbohydrate deficiency theory is the chief underlying factor in the causation of the vomiting of pregnancy as well as that of the other toxemias.

Adair states that vomiting of pregnancy conforms to no particular type and is not dependent on the taking of food and very often food is not vomited. He further calls our attention to the spongy bleeding gums, salivation, peculiar odor of the breath, epigastric distress, hematemesis and constipation, that may accompany the vomiting.

From a general consideration of these various theories concerning the etiology of vomiting of pregnancy, it seems most likely that a

metabolic disturbance, and in particular, perhaps, an upset in the carbohydrate metabolism which in turn leads to incomplete oxidation of fatty acids, plays a rôle in the different manifestations of this toxemia of the early half of gestation. These metabolic disturbances will be more fully discussed after we have considered the chemical changes accompanying this disease. Failure on the part of the mother to destroy foetal tissue that had entered the maternal circulation may be a further factor.

Urine and blood. In vomiting of pregnancy, the analysis of the urine does not show any marked disturbances of the nitrogen partition, except in very severe cases when we notice an increase in the ammonia coefficient. Williams was the first to observe this change in the nitrogen partition, and for a time regarded all patients suffering from vomiting of pregnancy with an ammonia coefficient of 10 or over as severely sick. Underhill and others, however, have shown that a high ammonia coefficient may be the result of simple starvation, and Williams endorses this view. Drennan and Hicks believe that there are two types of vomiting of pregnancy; the neurotic and the toxic; in the neurotic type of hyperemesis there is no increase in the ammonia coefficient in the urine, while a marked increase always accompanies the toxic type.

In a very careful study of the metabolic changes in vomiting of pregnancy, Dieckmann and Crossen could find no marked disturbances in the urinary components, except for a decrease in the chlorides. According to Stander, Duncan and Moses the excretion rate of urea is within normal limits. Cleisz and Laudat came to a similar conclusion. We may therefore conclude that analysis of the urine in vomiting of pregnancy has revealed no outstanding differences from the normal, except a high ammonia coefficient, which is probably the result of starvation.

Examination of the blood components has given us more specific information. According to Stander, the non-protein nitrogen and uric acid are usually increased in severe cases of vomiting of pregnancy. Harding and his coworkers, as well as Haden and Guffey, found in addition to an increase in non protein nitrogen and uric acid, an increase in urea. These authors also reported low values for sodium chloride. Harding regards the decreased chlorides as indicative of

dehydration. Dieckmann and Crossen report normal or occasional increased non-protein nitrogen and urea nitrogen and increased uric acid in the blood. Killian and Sherwin found increased non-protein nitrogen but decreased urea nitrogen in pernicious vomiting. The increased uric acid noted in their cases of vomiting of pregnancy they ascribe to an impairment of renal function. Plass and his coworkers have studied the partition of the nitrogenous products in the blood stream in the different forms of pregnancy, both normal and abnormal, but could find no significant changes in the protein fractions in vomiting of pregnancy.

Runge and Juhl report increased amino acids in vomiting of pregnancy. In normal non-pregnant women they found 27.3 mgm. per cent; in normal pregnant women 32 mgm. per cent and in cases of vomiting of pregnancy from 45 to 76 mgm. per cent. Increased lactic acid in the blood has also been observed by Loeser.

The blood sugar in vomiting of pregnancy has received a great deal of attention. Dieckmann and Crossen, in their very careful study of a large number of cases, reported that the blood sugar is within normal limits. Most authors have found this to be the case. Titus, on the other hand, believes that there is a hypoglycemia in vomiting of pregnancy, and he goes so far as to assume that this hypoglycemia is associated with the etiology of the disease. In this clinic we have been unable to substantiate Titus' findings and observe normal blood sugar values in vomiting of pregnancy. The sugar tolerance test has been used to determine the existence of any disturbance in the carbohydrate metabolism during pregnancy. Kermauner is of the opinion that in severe cases of vomiting there is a disturbance in carbohydrate metabolism, which is manifested by an abnormal sugar tolerance.

Bokelmann and Bock noted a marked increase in "acetone bodies" in 22 cases of vomiting of pregnancy. They divided their cases into three groups: (1) physiologic vomiting, in which the amount of acetone bodies in the blood is below 80 mgm. per 100 cc. of blood; (2) emesis gravidarum, in which there is more than 100 mgm. of acetone bodies per 100 cc. of blood; and (3) hyperemesis gravidarum, in which the concentration of acetone bodies in the blood is over 150 mgm. per 100 cc. They further believe that when the acetone bodies in the blood is 200 mgm. per 100 cc. of blood, we are dealing with a malignant form

of the disease. According to these authors, the increase in acetone bodies is due to an actual shortage in carbohydrates, a deficient metabolism of carbohydrates and a change in the fat metabolism. Vomiting of pregnancy leads to undernutrition and this in turn to decomposition of body substances. Rubner has shown that on maintenance diet there is only about 7 per cent more energy used than in hunger. With longer starvation, and after the carbohydrates have been exhausted, the fats and proteins of the body are called upon to furnish the required energy. In relative starvation the energy consumed probably follows the same principle as in actual starvation, protein being spared to the very last. While the protein is being spared, the fat is used up, and as a result of this increased burning of fat, the fat content of the blood increases and acetone bodies appear in the urine. Small amounts of glucose given in starving animals are enough to start a great amount of acetone bodies in the urine, and consequently an acetonuria follows more as a consequence of carbohydrate deficiency than as a result of inanition.

Ketosis, or an increased production of acetone bodies, may be induced in a normal individual by the ingestion of a salt-free or a carbohydrate-free diet. The complete oxidation of fatty acids depends on an ample supply of carbohydrates or antiketogenic substances. The ketogenic-antiketogenic ratio has not been carefully studied in vomiting of pregnancy, and it is probable that such an investigation may reveal a ratio exceeding the normal limits.

The acid-base equilibrium seems to be undisturbed in vomiting of pregnancy. Dieckmann and Crossen found even in severe cases of pernicious vomiting the hydrogen-ion concentration as well as the CO_2-combining power (compensated alkali deficit) to be essentially normal. Harding and Stander also report normal values for the plasma CO_2-combining power.

The most outstanding chemical changes, therefore, accompanying severe vomiting of pregnancy are a high ammonia coefficient in the urine, slightly increased non-protein nitrogen, decreased blood chlorides, and increased uric, amino, and lactic acids, with a marked accumulation of acetone bodies in the blood stream. Dehydration, starvation and incomplete oxidation of fatty acids following a high ketogenic-antiketogenic ratio, undoubtedly play the important rôle in the production of these chemical changes.

Treatment. As an outcome of the theory of Hirst that the corpus luteum plays an important part in relation to vomiting of pregnancy, extract of corpus luteum has been extensively used in the treatment of this disease. Hirst has reported a large number of cases successfully treated with this extract. Quigley reported 17 cases so treated, of these 12 were permanently cured, 4 improved and 1 not benefited. Coffey reports unsatisfactory results with dry extracts of corpus luteum, whereas good results followed the use of hypodermic injections of corpus luteum solutions.

Cary has employed the desiccated placenta in treating vomiting of pregnancy. He reports 13 cases with satisfactory results in 11. This author agrees that, if vomiting of pregnancy is due to a lowered immunity to the syncytium, as seems probable by the work of Acconi, the desiccated placenta may stimulate by acting as an antigen; and if the proteolytic ferment is lower, the desiccated placenta may increase the ferment content of the blood. He also believes that the placenta may be a gland of internal secretion, and so may activate the thyroid and adrenals and thereby hasten the oxidation of partially split products of protein which may be thrown into the blood stream.

According to Garnett, pernicious vomiting is probably a development of physiological vomiting of pregnancy, due to failure of the patient to produce a hormone antagonistic to the toxemia. He believes that the vomiting is caused by a poison and that the only satisfactory treatment so far developed consists in transfusion from post partum patients. This treatment has been used by others but with unsatisfactory results.

Pougert reports 4 cases suffering from pernicious vomiting and treated with their own blood. Corpus luteum and adrenalin were of no avail and after the patents had become very seriously ill, they received 20 cc. of their own blood mixed with 2 cc. of sodium citrate, and improvement followed.

Lynch is of the opinion that the formation of the nervous habit of vomiting accounts for the majority of cases of vomiting of pregnancy. He therefore tries to break this habit and treat the underlying cause of hyperacidity by medication and diet. The patient is put to bed, all food and drink by mouth is stopped until there has been no vomiting for twenty-four hours. The bowels are kept open, the patient is

given large doses of bromide as well as glucose and soda by rectum. Fruits and sweets are entirely contraindicated for many days and until the diet has been extended to include vegetables. Lynch believes that his results justify this treatment. In a personal communication to the author, Brindeau of Paris writes: "In the early toxemias (uncontrollable vomiting) I believe there is always a psychiatric basis. I always treat them by isolation and I no longer practice abortion."

Oldfield places his patients suffering from vomiting on an ordinary diet. This author is also of the opinion that all cases of vomiting of pregnancy are due to a neurosis and treates his patients accordingly.

X-ray treatments have also been tried in hyperemesis without convincing results. Fraenkel, however, is impressed by the success of x-ray therapy and reports 4 cases successsfully treated by x-ray application to the stomach. Luikhart proposed the use of luminal, stating that this drug always allays nausea and vomiting, and advised that it be administered hypodermically. In his hands this drug has proved successful in hyperemesis gravidarum, when intravenous corpus luteum and glucose and duodenal feeding had failed. Sieger starves his patients for three days and then gives them calcium with Ringer or normal saline solution together with bromides for the nervous system.

Duodenal feeding has been one of the recent methods of treatment. Haddock believes that the principle indication for the use of the duodenal tube is the loss of weight due to starvation or dehydration of the tissues. Schaick, on the other hand, thinks that the administration of water is the most important medication and that by supplying large amounts of water which is rapidly absorbed in the intestines, the patient usually gets well.

Davis reports a large series of patients suffering from vomiting of pregnancy treated quite successfully. His treatment in part is as follows:

"A careful history will usually reveal any previous gastrointestinal disturbance, or other physical conditions which might make the patient more sensitive to the disturbed metabolism of pregnancy. The physical examination will reveal any source of local irritation or infection. Drain the pus pockets or remove infected tonsils if necessary. Dental work must not be neglected during pregnancy. Try to correct a uterine displacement.

Treat acute cervicitis when present. Any of these may increase the nausea and vomiting, but are regarded as predisposing rather than causative factors.

"Cases approaching the pernicious stage require a special nurse and should be in a hospital. If seen early before marked dehydration and severe acidosis develops, stop all food and liquid by mouth and give 2 to 5 per cent glucose solution per rectum. Two hundred and fifty cubic centimeters of the glucose solution containing from 30 to 60 grains each of sodium bromide and sodium bicarbonate may be given as a retention enema every four or six hours. As the nervousness is controlled reduce the bromide to 30 grains. After twenty-four or thirty-six hours the patient may be allowed very small amounts of fluid and later solid food by mouth.

"Severe cases seen after marked dehydration is present should have 800 to 1000 cc. of N/NaCl under the breasts. If possible, should have an 18 or 20 per cent glucose solution in triple distilled water intravenously."

Since the work of Duncan and Harding in 1919 on the effect of high carbohydrate feeding in vomiting of pregnancy, there has developed a widespread interest in the use of carbohydrates in the treatment of this disease. Thalheimer advocates the use of insulin in the treatment of vomiting of pregnancy. He first used insulin in combating the acidosis following operations and then extended its use to the treatment of pernicious vomiting. He has reported some excellent results with the use of insulin. Following the work of this author, insulin has been extensively used in combating this toxemia. It is customary to give a protective dose of glucose with the insulin. It seems that this combined therapy of insulin and glucose relieves the ketonuria and acidosis, which usually accompanies vomiting. Thalheimer argues that there is a vicious cycle of acidosis causing vomiting and that the starvation following the vomiting causes further acidosis of a starvation type. He thinks that insulin breaks this cycle by enabling the body to oxidize the glucose, which in turn causes the burning of the products of incomplete fat metabolism, such as acetone, diacetic acid and B-oxy-butyric acid. Insulin and glucose have been used in many clinics and very satisfactory results have been reported. Titus, on the other hand, is of the opinion that glucose alone gives better results than insulin and glucose, and there has been quite a controversy in the literature as to the relative merits of these two methods of treat-

ment. Bokelmann agrees with Titus that insulin is a dangerous drug to be used in the toxemias of pregnancy.

Other German authors, however, such as Loeser, strongly advocate the use of insulin and glucose.

Vogt states that in vomiting and in eclampsia, as in hunger, there is glycogen starvation with increase in acetone bodies, a result of lack of carbohydrates or an abnormal metabolism of carbohydrates. The disturbance of carbohydrate metabolism is associated with a disturbance in protein metabolism, which shows an increase in ketone bodies and uric acid. He consequently uses insulin and glucose in the treatment of vomiting of pregnancy, believing that insulin alone is dangerous.

Mussey advocates a diet high in carbohydrates and a high fluid intake, with sufficient sedatives to raise the threshold of nervous irritability. In patients who show a low gastric acidity, he advocates the use of dilute hydrochloric aid, and in severe cases of vomiting intravenous injections of dextrose solution, together with insulin. Falkins is of the opinion that all women suffering from vomiting of pregnancy are undernourished and that it is possible to prevent vomiting in most cases by dietary measures. He consequently advocates increased carbohydrate nutrition.

The author has seen most of the methods enumerated above tried, and is convinced that there are a few cases which do not respond to any of these methods of treatment. There is undoubtedly a toxemic basis for vomiting of pregnancy, although the neurotic element should not be overlooked. From a clinical study and the chemical findings in the urine and blood, as well as from experimental work on animals, it seems to the author that all cases of vomiting of pregnancy are based on an underlying toxemia. In some women this toxemia may be so obscured by a predominating neurosis that one is almost entitled to make a diagnosis of neurotic vomiting. There is such a profound change in the metabolism during the early months of pregnancy that one might expect a certain percentage of patients to respond abnormally to this changed metabolism. We know that the foetus must get its food supply, and particularly its carbohydrates and protein, from the mother. From the work on the respiratory quotient of the foetus by Murlin, Stander and others, it is fairly well established that the

foetus utilizes mainly the carbohydrates for its energy requirements. This undoubtedly means a drain on the maternal carbohydrates, as is shown by the work of Bokelmann and his coworkers. The marked accumulation of acetone bodies must mean a profound disturbance of carbohydrate and fat metabolism. There can be little doubt that the changed metabolism accompanying pregnancy, which may so easily become perverted, as shown by the tendency towards acetonuria in pregnant women (Novak and Porges and others), is the underlying cause of all cases of vomiting of pregnancy. Apparently we do not know the starting point of this changed metabolism, but it seems rational that in the treatment we should endeavor to restore the patient to a normal metabolism. So far the best therapy to this end seems to be the use of insulin and glucose. When the vomiting has persisted to the extent of dehydration, and it is apparent that the tissues are urgently in need of water, one must undoubtedly immediately administer water, either in the form of saline or glucose solution intravenously, or by infusion, or by rectum.

When called to see a patient suffering from vomiting of pregnancy it is essential first to determine the severity of the disease, and whether starvation and dehydration have entered into the picture. If we are dealing with the results of starvation or dehydration or both, our therapy should be to introduce nutrition and water. If the disease has not developed to this final stage, it is advisable to determine how much, if any, neurotic element is involved and to treat the patient accordingly. It is of course essential that a careful clinical examination of the patient be carried out, in order to determine the presence or absence of such gynecological conditions as retroversion of the uterus, which, when present, should receive attention. Often the correction of such conditions leads to improvement.

As far as treating the actual vomiting of pregnancy is concerned, the author is of the opinion that the use of glucose or glucose and insulin, where indicated, and the administration of small but frequent meals, gives fairly satisfactory results. It is often advisable to starve the patient for twenty-four hours before instituting the therapy, and it is always necessary to enforce strict isolation. However, we must remember that in a small percentage of cases all therapy may be of no avail and a therapeutic abortion is inevitable. It must be pointed

out that we cannot lay too much stress on the value of complete isolation of the patient, especially from all relatives, and of suggestion.

II. Low reserve kidney

Though the term "low reserve kidney" may be inadequate and inaccurate, nevertheless, it describes a certain group of pregnancy toxemia cases perhaps as well as any other appellation so far suggested. In this group are incorporated many cases of "albuminuria of pregnancy." Albuminuria accompanies most of the toxemias of the latter half of pregnancy and it therefore appears both illogical and confusing to attempt to designate any one type of toxemia as "albuminuric." It is analogous to speaking of a "hypertensive" type of toxemia since the majority of women suffering from the various late toxemias of pregnancy have an elevated blood pressure. The term "albuminuria" should be reserved to denote a laboratory finding and no more. If this rule be followed in the future, it will not be such an impossible task, as it now is, correctly to interpret the meaning of the many authors using this word.

There is more justification for the use of the designation "recurrent toxemia." The only objection to it is that it does not tell us whether the process is benign or will become progressively worse with subsequent pregnancies. Either condition may be recurrent, but it is a matter of great importance for the physician to know whether the patient is suffering from a mild and benign toxemia or from a kidney condition which, if treated inadequately, may prove fatal in the near future. Furthermore, even eclampsia may be "recurrent." For these reasons the use of the term "recurrent toxemia" may be somewhat confusing to some of us.

Nephrosis as seen in the non-pregnant individuals, is a fairly definite entity and usually signifies a degenerative change in the tubules of the kidney. Mussey and Keith divide the acute nephritis occuring during pregnancy into acute glomerulonephritis and acute nephrosis, and state that while the former is associated with hypertension, oedema, oliguria and albuminuria, the latter differs from it in the absence of hypertension and changes in the fundi, and usually in the absence of erythrocytes in the urine and in the presence of oedema. From a clinical

and laboratory study, involving fairly complete urine and blood analyses, as well as kidney function and urea-excretion tests, of all toxemic patients in the Woman's Clinic of Johns Hopkins Hospital during the past six years, it appears to the author that we are not yet in a position to differentiate between acute glomerulonephritis and acute nephrosis occurring during pregnancy. It is for this reason, as stated earlier in this paper, that, in classifying kidney lesions associated with pregnancy, we believe the word "nephrosis" should be reserved until more is known about the behavior of the kidney during gestation.

This brings us to the term "low reserve kidney." It was only by studying repeated pregnancies occurring in the same individual that Stander and Peckham were able to differentiate the low reserve kidney from the other types of toxemias. This is the mildest form of late toxemia of pregnancy and usually manifests itself during the last two months of gravidity. These authors give the following as characteristic criteria:

"1. An elevated blood pressure, which at the end of the puerperium has dropped to a normal level. In most instances this elevation is not very marked, rarely exceeding 150 systolic and 90 diastolic.

2. The amount of albumin in the urine is never very great, varying before delivery between a fraction of a gram and 2 grams per liter, although the lower figures are most usually observed. The albumin disappears during the puerperium, and the patient leaves the service either with no albumin at all, or with at the most 0.1 gram per liter.

3. The outstanding characteristic is the fact that in subsequent pregnancies, the patient's condition does not become aggravated, and she is as well as, or better than, she was in the preceding pregnancy. Each of our 14 cases clearly demonstrates this point.

4. The blood chemistry as well as the urinary analysis reveals nothing abnormal.

That the number of pregnancies through which the individual may go plays any rôle in the development of this entity is very doubtful, for the reason that we observe it in primipara as well as in all degrees of multiparity. Moreover, this type of kidney does not seem to be permanently injured by pregnancy. As the woman approaches term a certain amount of albumin may pass through the glomerular membrane, the blood pressure become elevated, and some edema develop. With regard to the latter point it is interesting to note that in subsequent pregnancies there may be either no edema or at the most a slighter degree than before.

It is well known that in a healthy person, under normal conditions, all of the glomeruli are not functioning at capacity at any one time, and it has been estimated that there is usually a margin of safety which approaches 50 per cent. In other words, there is a decided kidney reserve which may be called into play. It therefore, seems resonable to suppose that in certain individuals such kidney reserve may be greatly decreased, due either to congenital causes or to factors which may have lessened the number of functioning glomeruli without producing a chronic nephritis. As we shall see in another group of cases, the strain of pregnancy always aggravates a chronic nephritis, so that later the kidneys are less well prepared to stand the strain of subsequent pregnancies. In the type of kidney under consideration this is not the case. All we can say is that the kidney reserve seems to be too low to meet the extra demands of pregnancy, as is manifested by the passage of a certain amount of albumin through the glomerular epithelium and by a moderate elevation of blood pressure, and that these manifestations usually disappear completely within two weeks after delivery. Furthermore, the kidney substance does not seem to have been injured by the pregnancy and the kidney reserve is certainly not lower in subsequent pregnancies. Such kidneys appear to be quite capable of functioning adequately while the woman is not pregnant, as well as for her and her fetus until about the eighth month of pregnancy, when manifestations of the low reserve kidney begin to make their appearance.

In addition to the 8 cases in our original paper, we have been able to find six more patients, who, during the period studied, had had a pregnancy with the typical signs and symptoms of a low reserve kidney, followed subsequently by a normal pregnancy. Such observations may be regarded as indisputable evidence that the occurrence of a mild toxemia in a given pregnancy is not necessarily followed by trouble in a subsequent one, and would accordingly indicate that the kidneys had not been permanently damaged."

The author proposes that this type of toxemia of the latter half of gestation be classed in our obstetrical clinics as "low reserve kidney" or as "recurrent toxemia," limiting the latter term strictly to the type of cases described in the preceding paragraphs. For the sake of uniformity this group will be referred to as low reserve kidney throughout all subsequent discussions in this paper.

Incidence. In this clinic in 253 women suffering from pregnancy toxemia during the years 1926 and 1927, low reserve kidney constituted

35 per cent of the total number. Likewise, a study of the histories of all toxemic patients treated in this Department since 1897 gave further evidence that from one fourth to one third of them suffered from this mild type of toxemia. Formerly a considerable proportion of patients with low reserve kidney were grouped as pre-eclamptic, and a smaller proportion as nephritic. From a study of the past history, blood pressure, urine-albumin, presence or absence of oedema, urine and blood chemistry, eye grounds, symptomatology and the duration of pregnancy, it is usually possible to make a correct differential diagnosis between low reserve kidney, chronic nephritis complicating pregnancy, and pre-eclampsia. This differential diagnosis will be disussed in detail after these other two types of toxemia have been considered.

Each year approximately 3 per cent of our toxemic patients fall into an unclassified group because the data at the time of discharge from the ward are insufficient for purposes of classification. In low reserve kidney the elevation of blood pressure and the albuminuria usually disappear completely two weeks after delivery, but in a very small fraction of cases it requires four to six weeks before the blood pressure becomes quite normal and the urine albumin-free.

As it is apparent that the outstanding manifestations of this toxemia are a slight elevation of blood pressure and a mild albuminuria it is advisable that we review some of the work on hypertension and albuminuria in pregnancy.

Hypertension and albuminuria. A slight elevation of blood pressure appears in a small proportion of all normal pregnancies. Irving studied the systolic blood pressure in 5000 consecutive cases of pregnancy, at the Boston Lying-In Hospital, and found that in 80 per cent the systolic blood pressure ranges between 100 and 130, and in 9 per cent falls below 100. In 11 per cent of his cases the blood pressure was 130 or over. This author believes that age, nationality and parity have an influence on the blood pressure; and that in the young person a high blood pressure is more frequently a sign of toxemia than in women over thirty years of age. His figures also show that an elevated blood pressure is more frequently an index of toxemia than is albuminuria, and is also an earlier sign.

Furthermore, the degree of elevation of blood pressure is of more significance than the amount of albumin in the urine, although both

are of great importance. Schulze states that the normal range of blood pressure during pregnancy is between 100 and 130 and that a systolic blood pressure of 150 or over should be regarded as an index of toxemia.

Donaldson studied the blood pressure in normal and abnormal pregnancy and came to the conclusion that during normal pregnancy there is no increase in blood pressure, nor does any fall in blood pressure occur immediately after labor. In cases of albuminuria complicating pregnancy, the most startling feature is the high systolic blood pressure.

Williamson states that hypertension may exist throughout pregnancy with no apparent sign of kidney disease. He believes that this type of hypertension is probably of vascular origin, caused by some toxic substance acting on the arterial wall. According to this author the prognosis in these cases is grave. Corwin and Herrick made a study of 165 cases of subacute or hypertensive type of toxemia of pregnancy, and found that 74 per cent showed cardiac hypertrophy, sclerosis of the brachial or radial arteries, vascular eye changes, or persistent elevated blood pressure after a period of from six months to six years post partum; and of these over one third showed persistent hypertension. Their investigations furthermore proved that in subsequent pregnancies the majority of women suffering from this type of toxemia will again exhibit hypertension, and they advise that such women should be observed over a series of years for evidence of cardiovascular disease.

Kylin in an extensive review of the question of hypertension divides all cases into two groups. To the first group belong acute diseases, such as glomerulonephritis, essential hypertension and arteriosclerosis, and to the second group the chronic conditions, such as contracted kidney. Hussey has reviewed all the disturbances, which may be associated with normal pregnancy, and believes that there are toxic substances of the amine type which may act upon the walls of the blood vessels, and that these substances have their origin in the placenta and perhaps also in such glands as the pituitary. Volhard has also described similar substances as sensitizing the vessel walls, making them particularly sensitive to pressor bodies. Hussey believes that these amines have a widespread action and that oedema is generally due to damage to the capillary walls resulting from the activity of these amines.

De Snoo groups the hypertension incident to gestation as follows: (1) hypertension associated with toxemia, (2) hypertension resulting from chronic nephritis, and (3) essential hypertension. His first group undoubtedly includes cases of low reserve kidney, as well as pre-eclampsia. The hypertension of chronic nephritis will be discussed later. Often we notice an elevated blood pressure without any other signs of toxemia. It is usual to regard this condition as essential hypertension. Essential hypertension is an idiopathic condition and we know very little or nothing about its etiology. If the patient had an elevated blood pressure without demonstrable disease before she became pregnant, it is probable that she is suffering from essential hypertension. On the contrary if her pressure is normal until about the middle of pregnancy and then begins to rise, it is undoubtedly due to a toxemic condition directly associated with the pregnancy and is not an essential hypertension. A great deal has been done concerning the therapeutic action of ions in the management of hypertension. Potassium sulphocyanate and iodine have given excellent results in lowering this type of high blood pressure.

Mussey and Randall agree with Irving that hypertension, especially in women under thirty years of age, is a better index of early toxemia than is albuminuria. They state that more than 25 per cent of primiparous women have a blood pressure over 140, and that such hypertension is a fair index of the onset of a toxemia. Wallich regards hypertension in pregnancy as related to functional disturbances of the kidney and autointoxication; this type of hypertension is accompanied by headaches, oedema, insomnia and polyuria, and may be responsible for placental hemorrhage.

Ginglinger divides all cases of albuminuria during pregnancy into four groups: (1) an unimportant group with only slight albuminuria; (2) albuminuria with little, if any oedema or hypertension; (3) albuminuria with much oedema and hypertension and (4) albuminuria without much oedema or hypertension but with marked nitrogen retention. For this classification we must know the percentage of albumin and the casts in the urine. Estimation of the chloride retention is judged by the amount of oedema, daily weight of the patient, the intake and output of water, the blood pressure and the blood urea.

Haffner examined the urine in 400 cases of pregnancy, and albumin

was found in 73 cases, or about 17 per cent. DeLee states that with the nitric acid test albumin will be found in only 3 to 5 per cent of gravidae, while it is far more frequently seen during the puerperium.

Pinard and Varnier believe that albuminuria is too often blamed on the state of pregnancy, whereas it may often be due to syphilis. They report cases of albuminuria during pregnancy where anti-syphilitic treatment caused the albumin to disappear from the urine. Cook suggests that the albuminuria of pregnancy may be due to mechanical pressure and resulting hyperemia, especially of the left kidney, but he has not been able to prove this. He calls attention to the post mortem findings and requests that we pay more attention to the vascular factors. According to Cattaneo the degree of azotemia and the salt content of the blood are of greater value in the diagnosis and prognosis of pregnancy nephropathies, than the albumin content of the urine.

Tangberg relates a case of albumosuria, in the seventh month of pregnancy. The patient had felt ill during the entire period of gestation. On admission there was no ablumin in her urine, her symptoms became worse and oedema and oliguria developed with albuminuria. Diet proved of no avail, and a few days later she gave birth to a still born infant, and all her symptoms immediately improved. The urine on admission, although containing no albumin, gave a positive test of albumose; and while the albumin disappeared from the urine on the 4th day postpartum, the albumose persisted until the tenth day postpartum. No extensive work has been done on the albumoses in the urine of pregnant women, and this may well be a fruitful field for future investigations.

For a long time it has been stated that placenta praevia and premature separation of the placenta may be associated with albuminuria and toxemia. Young and Miller reported that they found albuminuria in five of ten consecutive cases of placenta praevia and there were other symptoms of toxemia in three of the remaining five. They feel that the association between placenta praevia and toxemia is much more common than is at the present supposed. Danby suggests that the extensive extravasation of the blood into the pelvic tissue may be a manifestation of toxemia. He believes that the many hemorrhages which are almost pathognomonic of toxemia are due not only to in-

creased blood pressure but also to changes within the blood vessel walls, dependent upon a toxic substance producing the toxemia.

To summarize, low reserve kidney manifests itself in about 5 per cent of all full term pregnancies. It is a mild toxemia of the latter half of gestation, not associated with permanent or progressive injury of the kidneys, and not preceded by any renal damage. This toxemia may or may not reappear in a subsequent pregnancy, and if it does it is usually not more severe. The diagnosis is made on a moderate rise of blood pressure, usually about 150 systolic and 90 diastolic, and a relatively small amount of albumin in the urine, ranging from a fraction of a gram to 1 gram per liter of urine. These manifestations of toxemia appear during the last few months of pregnancy. There may also be some oedema, and very rarely a complaint of headache. Of great importance in establishing the diagnosis is the fact that by the end of the puerperium (three weeks after delivery) the blood pressure has resumed its normal level, the urine is albumin-free, and any oedema that may have been present, has disappeared. At no time do the blood constituents show any abnormality, and the nitrogen partition in the urine is normal. In subsequent pregnancies a similar picture may recur or the patient may be entirely normal. As to the etiology of this mild form of toxemia we are still in the dark.

Rest in bed and a low-protein diet will usually prove ample treatment for these patients. Occasionally oedema of the ankles and legs will disappear more rapidly after the restriction of salt in the diet. Improvement generally follows this type of treatment, and interruption of the pregnancy is not indicated. If, however, the condition becomes worse, notwithstanding rest in bed and proper dietary measures, we are most probably dealing with a chronic nephritis and not a low reserve kidney, in which case treatment may have to be more radical.

III. Nephritis complicating pregnancy

Many attempts have been made to classify the nephropathies of pregnancy. Perhaps the most generally used terms are chronic nephritis complicating pregnancy and nephritic toxemia. Acute glomerulonephritis, chronic glomerulonephritis, glomerulonephrosis, acute nephrosis (nephrosis), acute nephritis, chronic focal nephritis,

essential hypertension (benign hypertension) and malignant hypertension constitute subdivisions of nephritis. As there is such confusion in the use of some of these terms it is advisable that we clearly define each of them.

In glomerulonephritis the lesion is primarily limited to the glomeruli, resulting in hypertension, oedema, albuminuria, oliguria, hematuria and sometimes visual disturbances. The acute form is associated with a sudden onset, usually with normal renal function except for decreased excretion of salts and water, and very slight, if any, nitrogenous retention in the blood. The chronic type of glomerulonephritis differs from the acute in that the specific gravity of the urine is low and there may be evidence of nitrogenous retention with impaired kidney function. Glomerulonephrosis is a term suggested by Fahr to denote degenerative lesions in the glomeruli.

Mueller used the word nephrosis to designate degenerative changes in the kidney in contradistinction to an inflammatory process, and it now generally signifies a primary degenerative change as opposed to arteriosclerosis. Many authors regard nephrosis as a degenerative change limited to the tubules of the kidney. The term has also been used to denote oedema and perhaps albuminuria without hypertension or impaired renal function. High lipoid and low protein content of the blood serum, together with normal fundi, are supposed to be associated with nephrosis.

Acute nephritis is a vague term and does not classify the lesion, while focal nephritis, according to Volhard, denotes slight changes in the kidney of an inflammatory nature with albuminuria, hematuria and casts, but without impairment of renal function or oedema or hypertension.

Essential hypertension, as stated earlier in this paper, is of unknown etiology and may exist for many years without renal impairment. The elevated blood pressure is the only positive finding. In the so-called malignant type of hypertension the kidneys have become involved and a secondary nephritis is superimposed on the original benign hypertension. Wagener and Keith use the term malignant hypertension to denote vascular and retinal changes without impaired renal function.

Chronic nephritis is also subdivided into parenchymatous and inter-

stitial, the former presenting three types, the large red kidney, the large white kidney and the secondarily contracted kidney. This parenchymatous type is accompanied by general anasarca, headache, visual disturbance and albuminuria; chronic interstitial nephritis is also known as primary contracted kidney and is usually associated with arteriosclerosis and cardiac hypertrophy, and is characterized by polyuria with low specific gravity of the urine, and by albuminuria.

As a rule it is impossible to differentiate between the various types of nephritis during pregnancy. The added strain of pregnancy on the kidneys tends to obscure the diagnosis of any one particular form of nephritis. As we learn more about kidney function we may ultimately be able to establish such a differentiation, but at present we must content ourselves with the general diagnosis of nephritis complicating pregnancy, unless study before its onset has made it possible to distinguish the type.

Incidence. Nephritic toxemia, or the occurrence of pregnancy in a woman already suffering from chronic nephritis constitutes about 25 per cent of all gestation toxemias. In 3,330 consecutive deliveries in the Johns Hopkins Hospital, nephritis appeared as a complication of pregnancy in 61 cases; in other words, approximately two per cent. Cruickshank investigated a series of 23,630 cases admitted to the Glasgow Royal Maternity and Woman's Hospital during a period of ten years and found that the average incidence of nephritis was 2.84 per cent.

Symptoms. In their studies upon repeated pregnancies occurring in the same individual, Stander and Peckham found the outstanding characteristics of nephritis as a complication of gestation to be as follows:

"1. The last pregnancy shows more renal involvement than the one preceding it. Usually this is shown by the fact that a rising blood pressure and the presence of albumin in the urine are noted far earlier in pregnancy than was the case in the previous pregnancy. This is true for all of our patients except one, and even in that case there was a higher blood pressure and more albumin in the urine at the end of the puerperium following the second pregnancy than after the first pregnancy.

2. The nitrogen partition in the urine is often disturbed, the ammonia nitrogen increasing and the urea nitrogen being relatively less in amount.

3. In some cases nitrogenous retention in the blood becomes quite appreciable, as is shown by a rise in the nonprotein nitrogen, as well as in the urea nitrogen.

4. Edema is quite marked in a large percentage of cases and sometimes persists throughout the puerperium.

5. At the end of the puerperium following the last pregnancy the blood pressure, especially the diastolic, has not returned to the normal level; and there is usually some albumin in the urine.

The cases in this class can probably be divided into two subgroups, namely, those who had developed a chronic nephritis prior to the first pregnancy, or between pregnancies, from such causes as scarlet fever, tonsillitis, infectious diseases, myocarditis, or any of the conditions which may lead to chronic nephritis; and those in which repeated pregnancies may have played a rôle in the development of the nephritis. The past history of the patient will prove of value in determining such relations.

It is highly important that the obstetrician determine whether or not the toxemia falls into this group, for his advice to the patient and the treatment of the pregnancy will be governed accordingly. When there are definite signs of chronic nephritis it is unwise to allow the occurrence of further pregnancies, for each subsequent pregnancy leads to an earlier 'break' in the kidneys, and to more permanent damage to the renal tissue."

Kidney function. Several tests to determine kidney function have been developed during the past few years; of these the phenolsulphonephthalein test has been the most extensively used. Sonderer and Harvey, by means of this test, estimated the renal function in normal pregnancy and found a decreased excretion of the dye in the latter months of pregnancy. In the absence of renal lesions, they believe that it is due to a disturbance in the kidney function resulting from pressure exerted by the enlarging uterus. They emphasize the fact that the amount of dye excreted is the important factor in determining the function. We have used this test routinely for several years and have reluctantly come to the conclusion that it is not of much value in chronic nephritis complicating pregnancy.

Wallis proposed the urinary diastase test and believes that it gives conclusive evidence of renal insufficiency. In nephritis complicating pregnancy, he found consistently low values; while in all other cases of toxemia in pregnancy the test gave high values, which are usually much higher than normal. Most of the work on this starch-splitting

enzyme in the urine followed the observation of Wohlgemuth in 1909 that the amount of diastase is increased in pancreatic disease. Corbett found that a certain amount of diastase is present in normal blood and is excreted by the kidneys. Damage to the kidney epithelium results in an altered excretion of the enzyme. Schaanning used the formula

$$\frac{\frac{du \times D}{15}}{d_s}$$

to denote the ability of the kidney to concentrate diastase, (du is the diastase in 1 cc. of urine, d_s the diastase in the serum and D the amount of urine in twenty-four hours). He showed that in chronic nephritis the ability to concentrate diastase is reduced. Del Piano employed the same test as an index of kidney function during pregnancy, and states that where the kidney is normal there is less diastase in the blood serum than in the urine, while in cases of kidney damage the amount of diastase increases in the blood and decreases in the urine. Sepetinskaja determined the amylase index in non-pregnant and pregnant women, and in the first half of gestation observed values within the normal non-pregnant limits in 77.3 per cent of his cases, while in the remainder the index was higher. In the second half of pregnancy he found almost similar values, 81.9 per cent normal and 18.1 per cent higher. He does not agree with Wallis that nephritis may be differentiated from pre-eclampsia by means of a diastase test.

Many tests have been based on the excretion rate of urea, and most of these have followed the laws laid down by Ambard in 1909. His first law states that the urea excretion is proportional to the square root of the concentration of urea in the blood, other factors remaining constant; and, according to his second law, if the urea concentration in the blood is constant, the rate of urea excretion is inversely proportional to the square root of the urea concentration in the urine. Walker and Rowe in experiments carried out on normal and nephritic subjects found the first law of Ambard to be correct within only certain narrow limits, and the second law to be completely invalid.

In 1914 Marshall and Davis stated that in normal animals drinking water, the excretion is directly proportional to the concentration of urea in the blood; then McLean devised a formula based on the total

amount of urea excreted, the weight of the patient and the urea in the blood. In 1916 Addis and Watanabe concluded that the normal kidney under constant conditions possesses a very constant function, and Addis and Drury later developed their index, which is calculated on the amount of urea in one hour's urine expressed as a ratio of the urea in 100 cc. of blood. In 1921, Austin, Stillman and Van Slyke published their formula,

$$K = \frac{D}{B\sqrt{V\,W}},$$

where D is the urea output expressed in grams per twenty-four hours, B the blood urea, in grams per liter, V the volume of urine in liters per twenty-four hours, W the body weight in kilograms, and K the excretory constant. They found that K has a value of 7.5 to 3 for normal man. In 1924, Stander, Duncan and Moses proposed an index

$$X = \frac{B \times T.N.}{D}$$

where B is the urea-N in milligrams per 100 cc. of blood; $T.N.$ the total N in grams per twenty-four hours of urine, and D the urea N in grams per twenty-four hours of urine. These authors have been unable to obtain uniform results for the urea excretion rate with any of the above formulae, and therefore feel that the urea excretion rate is not of great value in differentiating chronic nephritis from the other types of pregnancy toxemia.

Rabinowitch, on the other hand, places great reliance upon the "urea concentration factor" and regards it as a more sensitive index of kidney function than the other tests generally used. The routine procedure, as described by Mills and Rabinowitch, is as follows:

The patient takes no food nor fluids of any kind after 7.00 p.m. the evening before the test. At 7.00 a.m. the day of the test the patient voids, and the specimen is discarded. The patient is then given 15 grams of urea dissolved in 150 cc. of water flavoured with lemon juice. The blood is collected two hours afterwards, and the urine one and two hours after the ingestion of the urea. The value of the factor is obtained as follows:

$$\text{Factor} = \frac{\text{milligrams urea per 100 cc. blood.}}{\text{milligrams urea per 100 cc. urine (second hour)}}$$

It appears scarcely necessary to reiterate that only by performing the test under the standard set of conditions described can the results be of real clinical value. The average normal value was found to be 40.

Since then an attempt has been made to measure, quantitatively, the efficiency of the kidneys, at least in so far as the excretion of urea is concerned—by the application of well recognized thermodynamic laws. The 'urea concentration factor' forms an essential part of this procedure. For theoretical purposes, as described, it was necessary to slightly modify the routine and calculation of the factor. This consisted in dividing the concentration of the urine urea, by the arithmetical mean concentration of the blood urea obtained both before and two hours after the ingestion of the urea. Thus:

$$\text{Factor} = \frac{\text{Urine urea concentration (second hour)}}{\frac{\text{Blood urea concentration before} + \text{blood urea after.}}{2}}$$

This increases the value of the factor from 40 to 50 for normal individuals."

Patch and Rabinowitch state that

"in lesions of the kidneys whether primarily or secondarily associated with azotemia or other evidence of impairment of the excretion of nitrogenous substances, the determination of the urea concentration factor is of greater value for diagnosis and a better index of progress than the individual consideration of either the blood urea nitrogen or urine urea concentration."

Clauser has modified the renal function test of Nyiri as follows: The bladder is emptied and the urine saved as a control. Ten cubic centimeters of 10 per cent sodium hyposulphite are injected intravenously and specimens obtained from the bladder in one, two, and three-hour periods. Twenty cubic centimeters of the urine are shaken up with half a gram of animal charcoal for two or three minutes and then filtered. To 10 cc. of the filtrate is added a little starch and then titration with 1/10 normal iodine solution carried out. The amount of iodine solution used, multiplied by 15.8, gives the amount of substance in 10 cc. of urine that is capable of binding iodine. He concludes that a definite decrease in renal function, which in normal pregnancy is very slight, becomes marked during labor; and that during the puerperium the kidney usually regains its function in less than five days. This test, he claims, is of value in nephritis complicating pregnancy.

Kingsbury and Swanson suggested a new kidney function test which consists in estimating the synthesis and elimination of hippuric acid. The patient is given sodium benzoate, 95 per cent of which is eliminated in the form of hippuric acid within three hours in the normal person. In chronic nephritis, the rate of elimination is the same, which proves that the kidney has little to do with the synthesis of hippuric acid. Their results show that this test varies in the same general direction as the phenolsulphonephthalein test but is capable of revealing abnormal renal conditions to a finer degree. Orlovius places great confidence in the estimation of creatinin and claims that where the clinical symptoms in nephritis during pregnancy are doubtful, the estimation of creatinin will give valuable information as to the prognosis. He uses the test of Neubauer in which creatinin dissolved in glucose is given by mouth, early in the morning, and the urine examined for creatinin at 6 hour intervals.

Harrison and Hewitt indorse the Andrewes Diazo test, although it and urea retention do not run strictly parallel. Bowen states that when the concentration of urea in the urine in the second hour is below 2 per cent, there is evidence of kidney insufficiency. MacKay and MacKay state that a patient with chronic interstitial nephritis may have a blood urea concentration within normal limits, even though only 50 per cent of normal functioning kidney tissue is present. Wittenbeck showed that the increase of uric acid in the blood does not depend on disturbances of kidney function.

Eckelt carried out a large series of tests on the kidney function during pregnancy, and observed no difference in the functional activity of the kidney in non-pregnant and pregnant women. In the so-called "kidney of pregnancy" there was an insufficiency only in the excretion of water and sodium chloride; and it is for this reason that he suggests that in the kidney of pregnancy, milk should not be used in the diet and advises a restriction in sodium chloride.

DeWesselow states that there are two distinct types of defect in renal function, namely, inability to excrete threshold substances, and inability to deal with non-threshold substances. As a typical example of threshold substances he mentions sodium chloride, and as a non-threshold substance urea, and states that defective elimination of sodium chloride is characteristic of hydremic or parenchymatous

nephritis, while in azotemic or interstitial nephritis there is an inability to excrete urea.

From the consideration of these various kidney function tests as well as from personal experience with certain of them in cases of pregnancy complicated with nephritis, it appears to the author that the urea concentration test, as developed by Rabinowitch and his coworkers, will prove the most useful in diagnosis and prognosis. The application of this test in a large series of toxemias may prove very instructive.

Chemical changes. Krauter investigated the hydrogen ion concentration of the urine in order to study the regulatory function of the kidneys on the acid base equilibrium during pregnancy. He concludes that the hydrogen ion concentration is more stable during pregnancy than in the non gravid state. The administration of acid or alkali does not change the acidity of the urine during pregnancy. From this the author concludes that the kidney function must be impaired, being less able to excrete the excessive amount of acid or alkali which may be present in the body. Rosenburg and Hellfors found that in renal insufficiency the acidity of the urine could not be changed by administration of alkali and believe that this is due to a disturbance in the acid base equilibra between tissue and blood. They also studied the urinary ammonia and found that in normal persons the ammonia decreases after the administration of alkali, whereas the opposite effect follows in cases of renal insufficiency. This they explained on the basis that in the person with abnormal kidneys there is a deficiency of alkali, and the administration of alkali results in setting free ammonia that has been used in the tissues for the neutralization of acids. Bloor, in his studies on blood lipoids in nephritis, noted a high fat in the plasma and corpuscles and high lecithin in the corpuscles, the cholesterol values being practically normal. He regards this abnormality as the result of a retarded assimilation of fat in the blood, which in turn is thought to be a manifestation of a general metabolic disturbance, brought about by a lowered alkali reserve of the blood and tissues.

Stander, Duncan and Sisson observed in nephritis only a slightly elevated uric acid but a definite increase in the blood urea nitrogen when expressed as a ratio of the non-protein nitrogen, as well as when ex-

pressed as a ratio of the urea nitrogen percentage in the urine. The latter ratio $\left(\frac{\text{B.U.N.}}{\text{U.N. per cent}}\right)$ is approximately 16 in normal pregnancy, while it rises to about 24 in nephritic toxemia. These investigators found that the inorganic elements were within normal limits in this type of pregnancy toxemia. De Wesselow in a clinical study of the toxemias of pregnancy noted that a definitely raised urea content of the blood, that is about 40 mgm. per 100 cc. of blood, is proof that the kidney is severely damaged, and affords an indication for interruption of pregnancy. Where there is no increase in blood urea, this author suggests that a urea concentration test be carried out, and, when the result is below 2 per cent, that pregnancy should again be interrupted. Dossena states that a differential diagnosis between nephritis and pregnancy nephropathy (low reserve kidney) can be made on the basis that urea in the blood is always increased in nephritis and never in nephropathy. In nephropathy there is an increase in chlorides and consequently water retention and oedema. Bunker and Mundell found a varying degree of nitrogenous retention in all their cases of nephritic toxemia. In a follow-up study of their cases, they were able to demonstrate a kidney lesion in some cases as late as two years after delivery.

Jackson, Sherwood and Moore attempted to corroborate the polypeptide nitrogen findings of Hulse and Straus, who had observed values as high as 30 mgm. per 100 cc. of blood in cases of hypertension. Hulse as well as Blau, gave the normal blood plasma polypeptide nitrogen as 3 mgm. per 100 cc. of blood. Jackson, Sherwood and Moore found the normal peptide nitrogen to range between 0 and 5.7 mgm., with an average of 0.8 mgm. In their cases of hypertension the peptide nitrogen ranges between 0.0 and 5.2 mgm., with an average of 0.7 mgm. They conclude that there is no direct evidence to show that in hypertension the peptide nitrogen rises sufficiently to be of prognostic significance.

Myers and Short studied 7 cases of nephritis with marked nitrogen retention and noted that there was no increase in the potassium content of the serum or of the whole blood, and believed that their observations do not lend support to the suggestion of Smillie that some of the symptoms of uremia may be due to a potassium poisoning. Denis and Hobson conducted a study on the inorganic constituents of

blood serum in nephritis and found a marked increase in the sodium chloride in 18 per cent of their cases; the inorganic phosphate fraction was increased in 45 per cent of the cases. They believe that sodium and chlorine are excreted with great ease even where the kidneys are badly damaged. Underhill and Wakeman produced severe nephritis in rabbits by sublethal doses of sodium tartrate, and noted a marked decrease in the chloride concentration of the blood and a corresponding increase in relative blood volume. With recovery the chloride concentration becomes normal.

In general, it may be said that in severe nephritis complicating pregnancy an elevated non-protein nitrogen, urea nitrogen and often a slight increase in uric acid will be found in the blood stream, but the absence of these abnormal findings does not exclude nephritis. The sodium chloride content of the blood, a renal function test, the patient's blood pressure, the amount of albumin in her urine, her past history, and the duration of pregnancy may all contribute in establishing the diagnosis.

Eye changes. The opthalmoscopic study of the eye grounds often aids in differentiating nephritic toxemia from other types of pregnancy toxemia. Albuminuric retinitis is sometimes seen in nephritis complicating pregnancy, while, according to Miller, it is never present in true eclampsia or pre-eclampsia. Wolff and Zade, in a clinical study of cases with marked renal disturbances, found that the definite forms of kidney disease in pregnancy could not be differentiated clinically, and state that albuminuric retinitis may be associated with ordinary "kidney of pregnancy" in the presence of a chronic nephritis.

Kollert states that hypertension and narrowing of vessels appear to be the essential factors in the origin of nephritic retinitis. With a falling blood pressure, healing may ensue. Deposits of cholesterol esters in the eye frequently occur with hypercholesteremia, but only when retinal disease is already present. Couvelaire reports two cases of retinitis without increase of the blood nitrogen, the retinitis occurring at about the fifth month of pregnancy. Complete blindness, albuminuria, and high blood pressure, were present in both cases, and each made a complete recovery after delivery of a six and a half and five months' foetus, respectively.

Rochet does not regard albuminuric retinitis as an absolutely un-

favorable diagnostic sign in nephritis. Fink states that in cases of acute blindness or severe amblyopia with normal eye grounds, the removal of the foetus becomes necessary only if uremia is present. On the other hand, visual disturbances of gradual onset are extremely serious. He furthermore believes that the theory of retinitis gravidarum occurring only with chronic nephritis is incorrect, and that this condition is often associated with a "kidney of pregnancy" and eclampsia. He does not agree with Schoeitz that patients with chronic nephritis and eye ground changes should be sterilized.

Capillaries. Following the fundamental work of Krogh on capillaries, some remarkable changes have been observed in the capillary walls in cases of nephritic toxemia. Nevermann, Hinselmann, Linzenmeier, Heynemann, and Niekan describe varying degrees of capillary stasis with changes in the size of the arterioles. Spasm of the walls of these small vessels has been noted and is supposed to be due to a toxic stimulation of the nervous supply or of the musculature of the vessel-walls. This capillary spasm, which can be observed in the nail-fold vessels, results in dilatation of other portions of the vessels, causing stagnation of the blood flow with resultant anoxemia. Mufson has studied the capillaries in a series of toxemias with hypertension at the Sloane Maternity Hospital, but found no consistently typical picture. He regards the presence of a high capillary pressure in these "hypertensive toxemias" as indicating an unfavorable prognosis for mother and child.

In normal pregnancy, Baer and Reis could find no abnormality in the capillary loops, neither as to morphology nor blood flow, but they observed elongation of the loops and increased tortuosity in cases of nephritis complicating pregnancy. In the latter condition the character of the capillary flow also showed abnormal deviations, so that the authors regard capillary microscopy as of value in differentiating true nephritis complicating pregnancy from the other toxemic conditions.

Kylin views nephritis occurring during pregnancy as practically identical with acute glomerulonephritis. In both conditions, he writes, the changes in the capillaries are identical, and the capillary pressure is raised. The modern tendency seems to be to regard nephritis as a systemic disease, rather than one strictly limited to the kidneys.

Prognosis. In this clinic during the past four years the immediate maternal mortality in nephritis complicating pregnancy has been 3.3 per cent, but it is evident that this figure does not give us a true concept of the severity of the disease. Every year we see women who had been discharged from the hospital a year or two previously, at the end of a fairly normal puerperium, succumb to chronic nephritis. We have no accurate method of determining the amount of damage to the kidneys done by the pregnancy. Jaschke, in discussing the prognosis of kidney disease in association with cardiac disease considers the condition very serious, and contends that labor should be induced as early as possible. It is only by reducing the work of the kidneys and the heart that the patient can be given any chance for the future. Hussey regards nephritis as a very serious complication of pregnancy, and is convinced that the gestation itself exerts an injurious influence on an already existing nephritis.

Very occasionally one may have to deal with cortical necrosis of the kidney, or with a nephrectomy preceding pregnancy. Manley and Kleinen reviewed the literature on cortical necrosis of the kidney in pregnancy, and found only 20 cases in all. Most of these were in the latter half of pregnancy, and usually associated with premature labor, and with stillborn babies. They reported the case of an eighth month pregnancy in a primipara, in whom the onset of the disease was very sudden. The case was complicated by severe hemorrhage and caesarean section was performed. There was total anuria for twelve days and the patient came to autopsy, where the characteristic lesions of cortical necrosis were seen. Rolleston also reports a case of symmetrical necrosis of the cortex of the kidney directly following childbirth. The symptoms in this patient resembled those of obstructive anuria. Necrosis of the cortex is probably intimately connected with thrombosis of the interlobular renal vessels.

Jardin and Kennedy studied 12 cases in which the suppression of the urine occurred as a complication of pregnancy. They found symmetrical necrosis of the renal cortex in 6 cases; in three of them there was evidence of pre-existing chronic inflammation, while in the other three the condition was cortical necrosis. But cortical necrosis of the kidney in pregnancy is so rare a condition that it need hardly be considered under the nephritic complications of pregnancy.

Matthews analyzed a large series of cases of nephrectomy and preg-

nancy and came to the same conclusions as Schmidt, who states that a woman with one healthy kidney does not run much greater risk, nor does the foetus, than the woman who has two healthy kidneys. Also Borelius states that normal pregnancy can follow nephrectomy without any difficulty, provided the remaining kidney is normal. Buschmann reports three cases of unilateral impairment of the kidney during pregnancy and suggests that pressure from the gravid uterus affecting the right kidney more than the left may play a part in the production of this impairment. He considers that the diminished renal function is due to primary venous stasis, just as one sees in advanced heart disease, as well as to direct pressure of the uterus upon the kidneys.

Treatment. From a consideration of the prognosis in nephritis complicating pregnancy, as outlined above, it will be clear that one assumes a grave responsibility by allowing gestation to proceed in the face of an underlying nephritis. Stander writes

"If the nephritic condition is severe, immediate termination of pregnancy becomes imperative. In the milder types of chronic nephritis rest in bed and dietetic treatment occasionally enable us to carry the patient to term without any serious harm to the mother, but it is well to remember that such an outcome is the exception rather than the rule. Furthermore, how can we be sure that the underlying renal condition has not been aggravated by the strain of the latter months of pregnancy, and that the patient's life has thereby been shortened, although this increased damage to the kidneys may not be apparent at the time of delivery? I strongly advocate the termination of pregnancy in all cases complicated by an underlying chronic nephritis, unless marked and rapid improvement follows the conservative treatment of rest in bed with restricted low-protein (and in some instances salt-free) diet and plenty of fluid. The patient's past history, both medical and obstetrical, the duration of the present pregnancy and the subjective and objective findings, enable us to form an opinion as to the severity of the nephritic condition."

Smith believes that a diet of lower protein content than is usually employed in the treatment of chronic nephritis, may be used in cases with nitrogenous retention. He bases the amount of protein allowed in the diet on the amount of non-protein nitrogen which the patient is able to excrete in twenty-four hours. The amount of protein nitrogen in the diet should be less than the total amount of non-protein nitrogen in the urine in twenty-four hours. Peters, on the other

hand, argues that in patients with albuminuria, the loss of protein must be indirectly compensated for by increasing the protein in the diet, otherwise a drain on tissue protein will follow. This is contrary to the usually accepted views that high-protein diet leads to kidney damage.

In nephritis complicating pregnancy the low-protein diet seems to give the best results as far as the dietary treatment is concerned. Where there is marked oedema, salt in the diet is contraindicated. As stated above, pregnancy should be terminated whenever there is no improvement on the strictly medical treatment and evidence of progressive renal damage is apparent. Too often the mother is subjected to further kidney injury, which may soon prove fatal, in order to obtain a living child; whereas the life of the mother should be our first consideration. Our attitude in this clinic has become more radical during the past five years, and if prompt improvement does not occur under conservative medical treatment, we terminate pregnancy by means of a bougie or bag and upon discharge from the hospital the patient is advised as to the use of contraceptives. Often it is advisable to terminate the pregnancy by caesarean section and effect sterilization at the same time especially where contraceptive advice will probably be ineffectual.

IV. Pre-eclampsia

The term "pre-eclamptic toxemia" has caused a great deal of confusion, as some writers have used it when referring to any one of the late toxemias of pregnancy. The author has advocated the discontinuance of this term and has suggested instead the word "pre-eclampsia," and furthermore that its use be limited to the relatively small group of cases in which the patient presents the signs, symptoms and laboratory findings of eclampsia but has not yet developed convulsions. In other words, pre-eclampsia is essentially eclampsia before the outbreak of convulsions and coma. Bar suggested that we designate eclampsia without convulsions as "eclampsism," which is undoubtedly synonymous with severe pre-eclampsia. When used in this restricted sense, pre-eclampsia is relatively rare, not exceeding five per cent of all the toxemias of the latter half of gestation, and occurring about fourteen times in every thousand deliveries, according to the figures of this clinic.

Pre-eclamptic patients usually show the same picture as eclampsia, except that convulsions are absent. The patient is acutely ill with a great amount of albumin and some casts in the urine and a high blood pressure. After delivery there is a prompt return to the normal blood pressure level and the urine soon becomes albumin free. The author believes that pre-eclampsia is a manifestation of the same disease entity as eclampsia, and differs from it only in so far as convulsions and coma do not occur. In other words, the pre-eclamptic patient has a potential eclampsia, being, as the name implies, in the stage preceding eclampsia. The disease develops usually during the last two months of gestation and its onset may be quite abrupt, as is so often the case in eclampsia. The first danger signal, especially where there has been no prenatal care, is frequently a complaint of sharp epigastric pain or failing vision. Within a short time the blood pressure has climbed to a high level, usually around 190 systolic and 110 diastolic. The urine contains three or more grams of albumin per liter, and there may be marked oedema of the face and extremities. Analysis of the blood reveals an elevated and steadily increasing uric acid content, and often a lowered CO_2-combining power. As a rule there is no nitrogenous retention, both the non-protein nitrogen and urea nitrogen being within normal limits. The blood sugar, the inorganic elements, calcium, magnesium, sodium, potassium and phosphorus in the blood, as well as the nitrogen partition in the urine, are usually within normal limits. Examination of the eye-grounds may show oedema of the retina, retinal hemorrhages or even detachment of the retina, but no albuminuric retinitis. If death does not occur during the attack delivery of the child is promptly followed by the disappearance of all abnormal findings within a week or two.

Mills states that the symptoms of headache, nausea and vomiting, epigastric pain and colonic distress are to be regarded as indicative of pre-eclampsia. According to this author the eyes are involved in about 90 per cent of all cases as a result of a physiologic enlargement of the pituitary gland. Different degrees of contraction of the visual fields by pressure upon the optic commissure and tracts are the result of this enlargement. He believes that the symptoms of pre-eclampsia arise from local intracranial pressure of the enlarged hypophysis as well as from increased function of this gland. He advocates that we separate the pre-eclamptic symptoms into those of pituitary origin and

those coming from a true toxemia of pregnancy, and that this can be done by a systematic examination of the visual fields and eye grounds. Dice finds that the first objective signs in the eyes of pre-eclamptic patients are a haziness of the fine detail of the fundus, a beginning retinitis; and he empties the uterus when this stage is present.

Klaften observed that the depth of respiration in pre-eclampsia is many times greater than in normal individuals, and he regards a rapid increase in the respiratory depth as a sign of an aggravation of the toxemia and as a warning of impending eclampsia. He also thinks the persistence of deep breathing after a convulsion is a very unfavorable sign.

Cary in discussing the etiology of pre-eclampsia states that a toxic substance or substances are elaborated which give rise to the syndrome of eclampsia and that this toxic substance is probably an early split product of the protein molecule. The source of the toxin is not single, and it may enter the maternal circulation in one of three or more ways, from autolysis of degenerating placenta, absorption into the large intestine of split products of bacterial origin, and from primary foci of infection. He was able, by extracting with normal salt solution placental tissues free from blood, to obtain a substance toxic to guinea pigs, when administered intraperitoneally. He could destroy the toxicity of this substance by incubating it with pregnant horse serum. He believes that these factors are suggestive that a substance is elaborated in the autolysis of the placenta which can produce eclamptic-like symptoms in experimental animals. This author has developed a method of treatment of pre-eclampsia, which consists in rest, increased elimination, and a salt-free, protein-free diet. Carbohydrates are given freely as well as buttermilk in order to change the intestinal flora from a putrefactive to a fermentative type. Sodium bicarbonate and in some cases calcium salts are administered in order to increase the urinary output and to decrease the irritability of the nervous system. Curl also believes in a low-protein diet in the treatment of pre-eclampsia.

The treatment of this type of toxemia varies greatly with different authors, depending on their views regarding the treatment of true eclampsia. Harding and Van Wyck are of the opinion that protein and fat produce no ill effects in the treatment of pre-eclampsia, but that salt in the diet is of main importance, as it always aggravates the

symptoms. The restriction of salt in the diet should not be continued for too long a period, and they determine the amount of salt in the diet by collecting twenty-four hour specimens of urine and finding the point at which the salt excretion reaches a constant minimum of 2 or 3 grams. They recommend the total restriction of salts one week in every four in addition to the usual prenatal care. Bland and Bernstein also advocate a salt-free diet in the treatment of this type of toxemia and report 13 cases successfully treated.

Mayer has treated 24 patients suffering from pre-eclampsia with ultra violet rays. The effect of this treatment is to lower the blood pressure and to decrease the amount of albumin in the urine. The rays are given from three to ten minutes at a time at a distance of 75 cm., and the treatment repeated. Only one of his patients developed eclampsia.

Peterson also regards pre-eclampsia as a type of intoxication which will end in convulsions, unless properly treated. He states that when, in spite of treatment, the albuminuria, cylindruria and blood urea increase along with a rise in blood pressure, and oedema, headache and eye disturbances become more marked, the uterus should be emptied. This author is an advocate of caesarean section but admits that each case must be judged by itself, taking into account the severity of the intoxication, the condition of the birth canal, and the size and condition of the child. Poucher is another advocate of caesarean section in pre-eclampsia.

From the work of Davis, Stander and others on anesthesia it seems advisable to the author that caesarean section under spinal or local anesthesia should be our method of choice in certain cases of pre-eclampsia, where the outbreak of an impending eclampsia appears imminent. Often the cervix is tightly closed, especially in primiparae so that the introduction of a bougie or bag with a long drawn out labor may do far more harm than a caesarean section performed quickly and without the use of a general anesthesia. If the pre-eclamptic patient does not improve promptly with rest in bed, restricted diet and sedatives, such as morphia and chloral hydrate, and we fear the development of true eclampsia, the patient should be delivered as promptly as is consistent with safety to the mother, and often a caesarean section under local or spinal anesthesia will give the best results in this type of case.

As the author regards pre-eclampsia simply as a stage in the develop-

ment of eclampsia, further discussion of its etiology will be given in the section on eclampsia. Likewise additional details regarding its treatment will be incorporated in the same section.

V. Eclampsia

"Eclampsia" is derived from the Greek ἔκλαμψις, meaning a shining forth or flash, and was first used by Hippocrates to denote a fever of sudden onset, and later by Sauvage. At the end of the eighteenth century, the German writer, Gehler employed the word "eklampsie," and gradually it came to mean a definite disease entity occurring during pregnancy. As used today, the term signifies an acute toxemia during the latter half of pregnancy or early puerperium, which is usually associated with clonic and tonic convulsions, followed by varying degrees of coma. It is perhaps more correct to define eclampsia as a symptom-complex, resulting from pregnancy, with cerebral phenomena as the most outstanding characteristic. Generally we regard eclampsia as synonymous with convulsions occurring during pregnancy, although eclampsia without convulsions is a recognized entity, sometimes corroborated in the postmortem room. Again, convulsions of epileptic, hysterical or meningeal origin, as well as those associated with uremia or acute yellow atrophy may occur during gestation, so that the appearance of fits does not necessarily mean the pregnant woman is suffering from eclampsia.

In the literature of the eighteenth century we find excellent descriptions of convulsions occurring during pregnancy or labor. Amberg, in 1713, described generalized convulsions in a pregnant woman, who was cured after the use of nervous powders and phlebotomy; undoubtedly an example of what we now know as intercurrent eclampsia. Many of the text-books on midwifery of the latter part of the eighteenth and early half of the nineteenth centuries contain detailed accounts of convulsions, or "epileptic fits" incident to child bearing, and ascribe them to various causes, such as uterine irritability, movements of the foetus, sudden emotions of the mind, excessive flooding or a blood plethora, and epilepsy. Alexander Hamilton in his "Elements of the Practice of Midwifery," published in 1775, writes

"1. Convulsions at an early period of Pregnancy chiefly happen to young Women of a plethoric sanguine habit, and can therefore only be removed or

palliated by a free and bold use of the Lancet, by an open belly, cool regimen, and spare diet. After plentiful evacuations, if the stomach be loaded with acrid Saburra or putrid Bile, a gentle Puke may be of use: But such remedies, on these occasions, must be employed with great caution. Instead of a Plethoric, if the Patient is of a nervous habit, a very necessary and important distinction, the intentions of cure will essentially vary. For here Opiates in large doses and frequently repeated, emollient clysters, stupes applied to the legs, the Semicupium, and every other means to soothe the nerves, and remove Spasmodic stricture, will prove the most effectual remedies. If insensible or comatous, Opium, Musk, and other Antispasmodics should be exhibited by way of clyster, and the Patient ought to be roused by Epispastic and stimulating Cataplasms applied to the legs and hams. Convulsions succeeding profuse evacuations, are generally mortal. The Vis Vitae, in such circumstances, must be supported, by replenishing the vessels with the utmost speed: This is to be done by pouring in nourishing fluids as fast as possible by the mouth, and by clyster; warm applications should also be made to the stomach and feet, and nervous cordials given internally along with Opium.

The treatment of Epileptic Fits, depending on other causes than those now mentioned, must be regulated by a proper attention to the particular symptoms with which they are attended.

2. In the advanced months, such Complaints are more to be dreaded than in early gestation, as they generally proceed from the irritation occasioned by the distention of the Uterine Fibres, or by the pressure of the Uterus on the contiguous Viscera: Hence the natural functions of these parts will be interrupted, the circulation of their fluids will be impeded, and the Blood, being thus prevented from descending to the inferior parts, will be derived in greater proportion to the Brain, and overcharge that Organ.

The Cure must, in this case, chiefly rest on copious and repeated Bleedings, an open Belly, and spare Diet.

3. Lastly, When Fits come on with Labour-pains, a speedy Delivery, if it can be done with safety, either by turning the Child, or by extracting with the Forceps when the Head is within reach, will prove the most effectual Cure."

Incidence. From a very careful study of all statistics published up to 1924, Hinselmann concludes that eclampsia occurs once in every 253.7 women entering a lying-in hospital, in other words in 0.39 per cent; while in private practice the frequency is one in 1816.6 or 0.05 per cent. The total incidence of eclampsia, according to this author, is one in every 867 births (0.12 per cent). Although the birth rate in

various countries differs markedly, and in some countries there are no figures as to birth rate, Hinselmann has estimated that with the world's population at 1,702 millions of people and the yearly birth rate at approximately 56 millions, the total number of eclamptic patients is approximately 64,570 per annum. Williams states that eclampsia occurs about once in every 500 labors, while in the lying-in hospitals the incidence is about one in every 130 deliveries or 0.75 per cent.

Zacheral observed 188 cases of eclampsia in 33,700 deliveries in the clinic at Graz, an incidence of 0.57 per cent, while Zweifel reports 190 cases of eclampsia in 29,733 deliveries in the Woman's clinic at Munich (0.64 per cent). The Hamburg Municipal Obstetrical Institute, according to Westphal, had 189 cases of eclampsia in 22,809 deliveries (0.83 per cent). Heinlein found among 14,000 deliveries, 253 cases of eclampsia, a percentage of 1.8; while Hingston and Mudalier also reported a high incidence of eclampsia, namely, 1.73 per cent, in the Government Hospital for Women at Madras, India. Nevermann found that in 385,226 births, eclampsia occurred 559 times, in other words, one in 689.13 births, a figure which corresponds fairly closely with that given by Hinselmann. Leidenius gives the statistics for 1911–1914 at the University Clinic at Helsingfors, and reports the total incidence of eclampsia as 0.6 per cent.

From these figures it appears that eclampsia occurs about once in every 500 to 800 deliveries; while the incidence in the obstetrical clinics is approximately one in every 150 births, because of the proportionally excessive number of seriously ill patients referred to hospitals for treatment.

Weather. Eclampsia varies in frequency at different times of the year and many authors have tried to demonstrate a connection between its incidence and weather conditions.

As early as 1825 Madame Lachapelle wrote that certain authors, Smellie among them, attributed a certain influence to the atmospheric conditions on the production of eclampsia. Schräder in 1882 and Olshausen in 1890 stated that eclampsia varied with the seasons. The latter observed 88 cases of eclampsia in the period of March to August and 105 cases from September to February. Glockner observed the greatest incidence from October to February. Knapp also observed the greatest incidence in the winter months. Schreiber, on the contrary, states that the greatest number of eclamptics occurs in the

months of July and August and the smallest number in November and February.

Croom from the statistics of the Edinburgh Maternity Hospital concluded that a sudden alteration in the temperature and rainfall, irrespective of any particular season, may affect the frequency of eclampsia. Hammerschlag in 1904 investigated the period 1898–1902 in East Prussia and could find no association between weather and eclampsia; while Linzenmeier found that eclampsia was especially frequent in the fall and in the spring and particularly on days with a sudden drop in temperature and northwest winds. v. Heuss made a very detailed study for the period 1908–1922 in Berlin and concludes that there are more cases of eclampsia on cold than on warm days, and that cold weather, fog and lowering temperatures are especially conducive to it. Hoenhorst, on the other hand, although he states that the incidence of eclampsia may possibly be enhanced by the effect of unfavorable weather on the excretory functions of the body leading to retention of toxins in the body, concludes that the weather is not a factor in the cause of the toxemia, but it may promote the onset of convulsions. Jacobs also states that eclampsia follows cold weather. Ragusa studied the incidence of eclampsia in Rome for a period of ten years but could find no connection between it and the weather.

Harrar, studying a series of cases of eclampsia at the New York Lying-In Hospital, found that the frequency of the disease was at its highest during the month of April, and that unsettled, damp and cold weather, as usually occurs in the spring months, is accompanied by an increase in the number of eclamptic patients.

There have also been studies to show that eclampsia is more frequent in large cities than in the country. v. Heuss thinks that the former tend to produce hypertension and so eclampsia, and consequently that it is primarily a disease of large cities. He found that in Germany 73 per cent of the fatal cases occurred in women of the industrial classes living in the large cities, as against 12 per cent living in the country, and attributes this variation to differences in diet and hygiene.

There also seem to be regional variations in the frequency of eclampsia. Ryan as early as 1831 stated that eclampsia is more frequent in England than in France. Madame Lachapelle found eclampsia to occur once in 567 in France, whereas in England according to the figures of Merriman, the incidence was one in 42. It is well known that

eclampsia is very common in Glasgow and its surrounding country. Hinselmann writes that in Germany, with a population of 60 million, there are about 2484 cases of eclampsia every year, while Eden reports the total incidence in Great Britain as 2800 among a population of only about 40 millions.

Influence of war. One of the interesting by-products of the World War, was the observation that the incidence of eclampsia was greatly reduced in the countries affected by the so-called hunger blockade, and gradually returned to the usual figure after the blockade was lifted. Thus Ruge reports that in the University clinic in Berlin, there were 15 cases of eclampsia in 1916 as compared with 45 cases in the year preceding the war. Mayer, Warnekros, Schülein, v. Jaschke, Zangemeister, Davidson and Miller, all report a lower incidence of eclampsia during this period. The figures of Warnekros are very indicative and are given in detail.

YEAR	BIRTHS	ECLAMPSIA	PER CENT
Universitäts-Frauenklinik, Berlin			
1910	1,476	62	4.2
1911	1,775	56	3.1
1912	1,868	59	3.2
1913	2,004	52	2.6
1914	1,994	51	2.6
1915	1,794	32	1.8
1916	1,430	12	0.8
Charité			
1912	3,320	78	2.4
1913	3,570	84	2.4
1914	3,350	66	2.0
1915	2,518	36	1.4
1916	1,400	8	0.57
Rud. Virchow-Krankenhaus, Wöchenerinnenheim am Urban, Wöchenerinnenheim Norden			
1912	2,942	57	2.0
1913	3,464	42	1.2
1914	3,496	40	1.2
1915	3,511	42	1.2
1916	2,462	25	1.0

Zangemeister made a very detailed study of this question and found that for the period January 1, 1911 to June 30, 1915, the incidence of eclampsia was 1 in 70, whereas during the period of July, 1915 to December, 1916, it decreased to 1 in 104. (These figures are based on the statistics of the various German clinics.) Hinselmann, on totaling all cases from lying-in hospitals reported in the literature, concludes that the incidence before the war was 1 in 69.5; during the war 1 in 118.4; and after the war 1 in 78.6. Furthermore, the total incidence of eclampsia throughout the country also showed a marked decrease during the war. The statistics for Baden indicate that the frequency before the war was 1 in 595; during the war, 1 in 961, and after the war 1 in 631.

Sachew also investigated the incidence of eclampsia by months during the years of the World War, and observed that it decreased greatly during the last years of the war, when the diet consisted mainly of carbohydrates. This author is of the opinion that meteorlogical conditions also had some effect on its frequency, because the wet months produced more cases, probably because of interference with the excretory functions of the skin. In Sweden, during 1917–1918, when there was a control of food supplies, Groene found a distinct decrease in the frequency of eclampsia. On the other hand, Bublitschenko, observing the cases of eclampsia for a period of ten years ending 1922, in Petrograd, Russia, noted that the incidence increased during the war, contrary to the findings in Germany, France and England, and this notwithstanding the revolution and long period of famine. His observations speak against the theory that the decrease in protein and fat, and the increase in carbohydrates in the diet was responsible for the diminished incidence.

Various reasons have been advanced to explain this lowered incidence during the World War, and the one most generally given is the change in character of the diet incident to the war. The women undoubtedly received a relatively low percentage of protein and fat, with a corresponding increase in carbohydrates, in contrast to the soldiers who were well fed.

But there were other factors, such as inefficient conveyance, and the crowded conditions of the hospitals, that may explain the lowered incidence of eclampsia during the years of the war. We know that

eclampsia is approximately many times more frequent among primiparae than multiparae, and it is possible that a change in the ratio of primiparae to multiparae might have taken place during the war. Hinselmann gives the figures for Baden, showing that such a change did not take place during the war.

Period 1905–1914 $\frac{\text{Primiparae}}{\text{Multiparae}} = \frac{14390}{51140}$, (Primiparae = 22 per cent).

Period 1915–1918 $\frac{\text{Primiparae}}{\text{Multiparae}} = \frac{7605}{26947}$, (Primiparae = 22 per cent).

Period 1919–1920 $\frac{\text{Primiparae}}{\text{Multiparae}} = \frac{18728}{35427}$, (Primiparae = 53 per cent).

From these figures it is evident that there was no greater relative decrease in primiparae than in multiparae during the war, and consequently the decline in eclampsia cannot be explained by a change in that ratio. Hinselmann's statistics for the post-war period are exceedingly interesting, and indicate that the marked increase in primiparae, from 22 per cent in 1915–1918 to 53 per cent in 1919–1920, should have resulted in a much greater occurrence of eclampsia than was actually observed. He reasons that the same factors which were responsible for the decline of eclampsia during the war, may still have been operating in the years immediately following it. The incidence of eclampsia in the post-war period is about the same as in the pre-war period, undoubtedly the result of two neutralizing factors, the great predominance of primiparae over multiparae tending to augment greatly the number of eclamptics, and the "war factor," in which diet perhaps played some rôle, tending to decrease the frequency of the disease.

In the clinic at Bonn, there was a slight relative increase in the number of primiparae during the war, and a still further increase in the years following the war. Also in the State of Hamburg, Hinselmann found an increase in the $\frac{\text{primiparae}}{\text{multiparae}}$ for the years following the war, as during 1917–1918 primiparae made up 34 per cent of the total deliveries, while for 1919 to 1922 this percentage increased to 50.

Parity. As early as 1768 Denman observed that there was a differ-

ence in the incidence of eclampsia among primiparae and multiparae. Velpeau in his text-book, published in 1835, states that eclampsia is more common among primiparae, and quotes Merriman as reporting 36 cases of eclampsia in primiparae, as against 12 among multiparae. All writers on midwifery from that time on have recognized this fact; and recently Zangemeister, in studying a large series of deliveries found 442 cases of eclampsia in 92,122 primiparae, as compared with 180 among 291,718 multiparae, an incidence of 1 in 209, and 1 in 1621 respectively. Hinselmann, likewise, has aggregated the figures of Lantos, Knapp, Bidder and Spitzbarth and estimates the frequency of eclampsia at 1 in 68 primiparae and 1 in 400 multiparae. Although the figures of the latter author show a generally higher incidence, the ratio of primiparae to multiparae is approximately the same as given by Zangemeister.

Types. Eclampsia may occur during pregnancy, labor or the puerperium. If it occurs before the patient has reached term, is followed by recovery, with normal labor subsequently, it is called intercurrent eclampsia, a term introduced by Lichtenstein. If the patient is not in labor, we designate it antepartum eclampsia; if it supervenes during labor, intrapartum eclampsia, and if during the puerperium, postpartum eclampsia. The relative incidence among these three types, antepartum, intrapartum, and postpartum varies greatly, and it is generally stated that the antepartum and intrapartum types are the most frequent. Schröder in 1882 stated that antepartum eclampsia formed 19.6 per cent of all cases. Schaute gave 13.5 per cent for antepartum, 59.8 per cent intrapartum and 26.7 per cent postpartum. Olshausen found 30 per cent antepartum; 56 per cent intrapartum and 14 per cent postpartum. Williams, on the other hand, gives the greatest frequency for antepartum eclampsia, and Eden holds similar views. The former gives an incidence of 55, 22 and 23 per cent for the three types respectively, and the latter, 61.5; 19.2 and 19.3 per cent. Hinselmann, in summing up the figures from all available sources, found antepartum eclampsia in 26 per cent, intrapartum in 53 per cent, and postpartum eclampsia in 21 per cent. Williams comments on this discrepancy, and states that most writers fail to remember that eclampsia usually appears before the estimated date of delivery and that uterine contractions frequently set in with

the first convulsion; in other words, he contends the eclamptic seizure may produce labor, and although the patient is in labor when first seen, the eclampsia had actually antedated the labor and is therefore of the antepartum variety. This appears to be a valid argument, and we are probably safe in concluding that about one-half of all cases of eclampsia are of the antepartum type, and that the other two forms, intrapartum and postpartum, are approximately of equal frequency.

Multiple pregnancies are viewed as predisposing factors in the outbreak of eclampsia. As early as 1824, Miquel-Cerutti regarded hydramnios, monstrosities and multiple pregnancies as causative factors in the development of eclampsia. Williams writes "twin pregnancy and hydramnios appear to act as predisposing factors in the development of eclampsia." Zangemeister states that while in normal individuals, multiple pregnancy occurs once in 79 births, in eclamptic patients it occurs once in 15 births; in other words, five times more frequently than in normal pregnancy. Likewise, Hinselmann, in a comprehensive series of 7645 cases of eclampsia, found that multiple pregnancy occurred once in every 15.7 cases; in other words, an incidence of 6 per cent. Bumm states that multiple pregnancy and hydatidiform mole predispose to eclampsia, but hydramnios does not.

Age and mode of living. Studies have been made to attempt to ascertain the relationship between the occurrence of eclampsia and the age of the patient. Shröder, in 1882, wrote that there is no age limit for eclampsia. A summary of the figures of Buttner, Bidder, Hammerschlag and Spitzbarth, shows that 90.2 per cent of all cases of eclampsia occur between the ages of 14 and 30, and 9.8 per cent after 30 years. Schauta observed that most of his eclamptics occurred before 30 years of age, and that the age of predilection is between 21 and 25 years of age.

We have already noted that eclampsia occurs about 8 times more frequently among primiparae than multiparae, and when it is borne in mind that the majority of first pregnancies fall between the ages of nineteen and twenty-four years, we can readily see why the incidence of eclampsia is so very high at that period.

There is some difference of opinion as to whether the mode of living has anything to do with the incidence of eclampsia. The older authors were of the opinion that it occurred less frequently among the poor

people than the well-to-do. Bard, in 1815, wrote that women "in the higher spheres of life, who have been delicately bred and who indulge themselves in a dissipated and luxurious life, are much more liable to these dreaded and fatal diseases than the hardy inhabitants of the country." We agree with him that eclampsia is more frequent in the large cities than in the country.

Gehler in 1798 said that eclampsia is particularly common among the delicate city women who have a disposition towards this disease, acquired by heritage or as a result of their sedentary mode of living, avoiding every act they are not accustomed to; and that the disease is rare among the country classes. Velpeau and Bluff, in 1834, expressed similar views.

In our own times, Hammerschlag found eclampsia more frequent in the cities than in the country and estimates that there is only one eclamptic for every 1800 births in the latter as compared with 1 in 286 in the former.

Gessner has called attention to the fact that during the war, women did more work than before the war, and that better nutrition fostered by a more active life may have been a factor in the lowered incidence of the disease during the war.

Erroneous conclusions may easily be drawn as to the effect city-life, country-life, or the mode of living may have on the incidence of eclampsia, because of factors that do not lend themselves to ready investigation. Many patients are referred from the country to the city doctor for delivery; record of disease or cause of death is often incomplete in deliveries outside the hospitals, and the exact manner of living of the patient is often not known. Nevertheless, Kosmak is probably fully justified in saying that "eclampsia is as prevalent among the poor as among the well-to-do. It is probably even more prevalent among the poor, unless proper supervision is maintained," and our experience is that in Baltimore it occurs most frequently among ignorant negroes who are too unintelligent to take advantage of the opportunities for efficient prenatal care.

Recurrence. Eclampsia may recur in subsequent pregnancies, although the disease undoubtedly confers a relative immunity. Denman in 1768 noted that eclampsia recurred in certain women. Bumm, in the last edition of his text-book, wrote that about ten per cent of

eclamptic patients have a second attack in a subsequent pregnancy. He differentiates between "widerholte Eklampsie" and "rezidivierende Eklampsie," the former denoting the occurrence of eclampsia in the same individual in a subsequent pregnancy, while the latter means repeated attacks of eclampsia during the course of a single pregnancy.

Williams writes "In my experience, a woman who has had eclampsia is less disposed to the disease in future pregnancies, than one who has never had it."

Hinselmann collected all available statistics on this question, and came to the conclusion that there is a recurrence in only 1.92 per cent, or, to express it another way, he states that in 10,000 cases of eclampsia recurrence in subsequent pregnancies will be noted in 192.

Early and late eclampsia. Although eclampsia usually occurs during the latter third of pregnancy, the disease has been observed in the first half of pregnanc . Ebeler, in 1911, collected from the literature on eclampsia, 55 cases which had occurred during the first half of pregnancy, and Bourne reported a case at the twenty-fourth week of pregnancy. Füth in 1928, reviewed the cases of early eclampsia already recorded, and reports a case of his own at the fourth month, which at autopsy showed typical eclamptic liver lesions and glomerulonephritis. His patient was twenty-two years old, and in the fourth month of her first pregnancy she developed two convulsions. A dead foetus was removed, and the convulsions recurred. The patient died five and three quarter hours after the first eclamptic convulsion. At autopsy it was found that there were no gross lesions in the brain, and only slight changes in the liver and kidneys. Füth believes this to be a case of true eclampsia.

In a personal communication, E. D. Plass described a case of eclampsia in the early half of pregnancy. The patient, aged sixteen, white, was admitted to the hospital after having had 17 convulsions and having been semi-comatose between attacks. The convulsions were preceded by epigastric pain and vomiting. She was treated conservatively along the lines proposed by Stroganoff, and improvement followed. A macerated fetus was passed seven days following the last convulsion. Plass sums up the patient's history as follows: "It would seem that a diagnosis of eclampsia is justified on this patient. The history of convulsions is clear, the patient was admitted in coma,

there was albumin in the urine, and the fetus apparently died at the time of the attacks. The absence of oedema, the normal blood pressure and the fact that there were no convulsive attacks after admission do not seem to me to overweigh the other positive facts. It is regrettable that the patient did not remain in the hospital for further kidney function tests."

Eclampsia has also been reported as occurring weeks and even months following delivery. To my mind it is extremely doubtful whether convulsions appearing four days or more after parturition can be considered due to postpartum eclampsia, and hysteria, epilepsy or meningitis usually will be found to be the underlying cause in such cases. Most, if not all, cases of postpartum eclampsia occur within the first two days following labor.

Constitution. For many years it has been thought that constitutional factors may predispose toward the development of eclampsia. Early references to this may be found in the work of Bluff, Naegele, Späth, Höhl and Scanzoni. In 1891 Schröder wrote: "Es schützt kein Alter und kein Stand vor der Eklampsie. Schlechte Ernährung und Anämie geben keine Disposition dazu, im Gegenteil sind es besonders häufig vollblütige, mit starkem panniculus adiposus versehene Erstgebärende."

Hinselmann states that both delicate (zarte) and strong women may have eclampsia, and that no outward body appearance seems to be a predisposing factor in the development of eclampsia. On the other hand he believes that the structure and function of the different organs of the body, considered as a whole, may give us information as to its incidence, and lays stress on the hemopoietic system, and particularly the vascular volume. Brugsch estimates the heart volume from the transverse diameter of the heart, as measured by the X-Rays. The heart volume is supposed to bear a definite relationship to the trunk volume, and the latter may be estimated by the formula:

$$\frac{\text{Trunk length} \times (\text{chest circumference})^2}{4\ \pi}$$

Normally the heart volume should be from 1/50 to 1/34 of the trunk volume. Although the heart volume may not actually be smaller in eclampsia, Hinselmann believes that the total vascular volume may be

a factor in the production of eclampsia, and has developed a formula to express such a probability. He starts with the equation of Hueppe and Brugsch, which states that the illness equals $f\ (C.p)$, where f is a constant, C the constitution and p the agent producing the disease. Since pregnancy is the agent responsible for the eclamptic state, eclampsia $= f\ (C.S.)$, where S represents pregnancy.

Hinselmann further modifies this formula so that finally,

$$\text{Eclampsia} = f\ \{(S_o \cdot W_f) \cdot Mg_f \cdot a_f \cdot (Mx)_f ?\}$$

where S represents pregnancy; W, labor pains; Mg, vascular system; a, outside circumstances; Mx, possible impaired function of other organs; o, indispensable factors; and f, optional factors.

Bublitschenko recently made a constitutional study of a large number of eclamptic patients and found that they present certain constitutional characteristics, such as small stature and great body weight. Jsaaksohn, as well as Sserdjukoff and Melnikoff observed that eclampsia was particularly common in the so-called pyknic type (large head, chest and abdomen, with tendency to obesity, and relatively small extremities). Sserdjukoff and Melnikoff found that 3.5 per cent of pregnant women belonging to the pyknic group had eclampsia, and that the disease was also quite prevalent in the athletic type. According to these authors, a comprehensive study of the significance of constitutional factors in pregnancy, labor and the puerperium shows that eclampsia is many times more common in blondes than brunettes.

Aschner believes that the plethoric type is especially prone to eclampsia, and regards the diseases as resulting from a further development of the plethora and dyscrasia of normal pregnancy. He states that the three factors of first importance in the causation of eclampsia are: (1) extreme grade of plethora, (2) extreme degree of pregnancy dyscrasia (acidosis), and as a result (3) increased reflex irritability (pregnancy spasmophilia).

Mortality. Frankel in a paper entitled "The Present Status of Maternal and Infant Hygiene in the United States" giving the mortality figures for 17 states and the District of Columbia, or what is called the United States Birth Registration Area, states that the maternal mortality for 1917 was 663 deaths per 100,000 live births, and that for 1924, the figure was about the same. This means a total maternal

mortality of 1 in 150. Eclampsia and allied toxemias accounted for 165 deaths per 100,000 births, or approximately 1 in 600. Baker, in 1927, wrote that 27 per cent of maternal deaths in the United States are due to puerperal albuminuria and convulsions, while MacMurchy states that 22 per cent of the deaths in Canada are due to the toxemias of pregnancy. Frankel estimates that approximately 17,000 women die in the United States every year as the result of child birth, and as the toxemias account for about one-fourth of the total maternal mortality, we may conclude that between 4000 to 4500 women died each year from the toxemias of pregnancy.

This figure includes death from vomiting of pregnancy, chronic nephritis complicating pregnancy, acute yellow atrophy of the liver as well as eclampsia; and as eclampsia is responsible for about 60 per cent of the total, it is evident that it accounts for about 2500 maternal deaths a year in this country, a figure which is identical with that given by Burns in 1926. Provided the incidence and average mortality rate in eclampsia in all other countries is the same as in the United States, this would indicate that about 30,000 women die annually from eclampsia throughout the world. Should we take the incidence of eclampsia as given by Williams, namely 1 in 500, it would mean that in 56,000,000 births, the total number of eclamptic patients is 110,000 a year with a total maternal mortality of 30,000 or 27.3 per cent.

The maternal mortality in eclampsia varies in different clinics and in different countries and this will be taken up more specifically in discussing the treatment; but it seems to be a safe estimate that the maternal mortality rate approaches 25 per cent throughout the world.

Pathology. In 1843 Lever demonstrated that the urine of eclamptic patients contained albumin, and this led to the theory that kidney lesions were always associated with eclampsia. Traube and Rosenstein regarded the kidney changes as resulting from pressure of the pregnant uterus on the renal veins. Later Schröeder, Ingerslev, and others reported cases of eclampsia without albumin in the urine so that the uremic origin of the eclamptic convulsion had to be abandoned.

Autopsy will usually reveal the presence of renal changes, but the lesions are generally those of degeneration of the epithelium of the convoluted tubules, according to Williams. Prutz observed kidney changes in over 95 per cent in a series of eclamptic patients who come

to autopsy, but is of the opinion that the kidney lesions play a secondary part in the production of eclampsia, as they are for the most part too slight to be of great significance. Schmorl, Barr and others hold a similar view. Heynemann, on the other hand, is a strong advocate of the theory that kidney lesions are fundamental in the etiology of eclampsia. He believes that the condition in eclampsia is identical with the so-called kidney of pregnancy. Watson studied three cases of eclampsia and found profuse glomerulonephritis in all. Fahr has given an excellent résumé of the literature covering the kidney changes in eclampsia. In his own cases of eclampsia he observed renal findings suggesting a tubulo- and glomerulo-nephritis, in other words, primary degenerative changes in the tubular epithelium and glomeruli, as well as degenerative changes in the arterioles. He summarizes the pathology of the kidney in eclampsia as follows: (1) swelling of the glomerular loops, (2) albuminous degeneration of the epithelium, (3) degenerative (inflammatory) changes in the arterioles, (4) thrombotic processes in the vessels, especially the glomerular capillaries, (5) hemoglobin cylinders.

He further differentiates between the primary inflammatory processes, such as glomerulonephritis, in which there is a primary inflammation of the glomerular capillaries, and the kidney of eclampsia, as he does not regard the latter of an inflammatory nature.

Schwarz found similar changes in the kidney of eclampsia, swelling of the glomerular loops, albuminous degeneration of the convoluted tubules, hemoglobin cylinders, degenerative changes in the vessels and thrombi in the glomerular loops. He holds that the changes in the glomeruli are of chief interest, and seem to play the greatest part in the kidney lesions. The lumina of the glomeruli are narrowed as the result of the swelling and the vascular loops appear to be devoid of blood. Hyaline changes also occur, as well as fat depositions.

Although most cases of eclampsia present renal changes when studied in the autopsy room, it does not seem that the kidney lesions are characteristic of the disease, and are probably more the result than the cause of eclampsia. Furthermore, in patients who recover, the prompt return of the urine to normal inevitably indicates that the renal changes must be relatively trifling.

It is generally considered that peripheral necrosis of the liver

lobule is a characteristic lesion of eclampsia. Pilliet in 1888 described this hemorrhagic lesion in the liver of patients dying from eclampsia. His work was confirmed and elaborated in 1893 by Schmorl, who found typical lesions in the liver in every case of eclampsia studied. Williams, Opie and others regard areas of necrosis involving the periphery of the individual lobules and the portal spaces as characteristic of the disease, and do not hesitate to diagnosticate it merely from the presence of the lesion. At the same time they admit that the lesion is sometimes lacking in patients who have died from what was clinically eclampsia. For this reason they consider the lesions as a secondary manifestation, and not as the cause of the disease. In a recent article, Bell throws doubt on this concept and states that there is little agreement in the liver lesions in eclampsia. He observed passive congestion, localized infiltration, acute yellow atrophy, infarction, hemorrhagic necrosis, and cellular infiltration of the portal spaces in his cases, but found no typical lesion in all of them. He concludes that eclampsia is not dependent upon any one type of hepatic lesion. Levy-Solal and Tzanch are also of the opinion that the pathological findings in eclampsia are not characteristic and constant, and they consider that eclampsia is not caused by renal or hepatic disorders.

Fahr describes the liver of eclampsia as presenting typical changes localized in the periphery of the lobules, which are identical with those described by Schmorl, and which are characterized by the appearance of thrombofibrin in the portal capillaries, or capillary stasis, and the formation of blood spaces and hemorrhages, with cell destruction of the parts involved. Degenerative changes in the parenchyma, such as hyaline and fatty deposits, vacuolization, lymphocytic infiltration and more rarely bile stasis and small bile thrombi are also seen.

The brain has been carefully studied in many cases of eclampsia. Oedema, hyperemia, anemia, thrombosis, and softening are among the findings reported. Galy-Gasparrou and Labor report a case of eclampsia in which the brain was very carefully examined, and in which they found small hemorrhages under the pia-mater and large hemorrhages at the falx-cerebri, with small clots in the ventricle. Although it should be remembered that Volhard thirty-five years ago had directed attention to similar changes, Levant and Portes state that the pathology of the hemorrhages in the brain associated with

eclampsia is obscure, and that no distinct case of medullary hemorrhage associated with eclampsia has been described.

It has also been supposed that the ureters show pathological findings in eclampsia; Halbertsma first pointed out that the ureters are often enlarged and dilated in eclampsia and supposed that the condition played an etiological part. Prutz, however, noted that the ureters were abnormal in only 37 cases out of 500 autopsies, and as this incidence is not much greater than in normal pregnancy, we agree with him in holding that dilatation of the ureters plays no part in the production of eclampsia.

Polak in analyzing 102 autopsies on eclamptic patients, found that the heart was involved in 94. The change usually consisted in a degenerative process of the myocardium, as described by Schmorl; but these are the results of the disease and not characteristic or pathognomonic.

Giant cells have been demonstrated in the capillaries of the lungs, and have been identified as masses of syncytium. Schmorl supposed that giant cells were associated with the etiology of eclampsia, but as they can always be found in the lungs of pregnant women dead from any disease, this view is no longer tenable, and their presence is assumed to be a result of deportation, which is now regarded as a coincident of every pregnancy.

Williams states that the main lesions in eclampsia are found in the liver, kidneys, heart and brain, but that with the exception of the lesions in the liver, the anatomical changes are not constant and characteristic.

Etiology of eclampsia. Zweifel has called eclampsia the "Disease of the Theories" and today this is still true. The earlier theories regarding the etiology of eclampsia are fully discussed in the various text-books on obstetrics, and will be referred to only briefly in this paper. In the 17th and 18th centuries eclampsia was regarded as a disorder of the nervous system.

In 1820, Merriman, writing about its etiology, regarded an overloaded state as the cause of eclampsia. In 1833, Wilson suggested that there was an association between an increased content of urea in the blood stream and eclampsia.

In 1840, Rayer described albuminuria and when a few years later,

Lever and Simpson discovered albuminuria in eclampsia, there developed the uremia theory of eclampsia. Freirichs believed that the sudden destruction of the urea in the body was its cause.

The following are some of the theories advanced: 1, Auto-intoxication. 2, Foetal elements. 3, Foetal metabolic products. 4, Placental products. 5, Bacterial invasion. 6, Endocrine disturbances. 7, Biological reactions. 8, Alterations in maternal metabolism. 9, Mammary toxemias. 10, Diet. 11, Amniotic fluid. 12, Physical chemical changes.

a. Auto-intoxication. Bouchard (1887) was the first to speak of intoxication or auto-intoxication and believed the blood of eclamptic women to be more poisonous than that of normal persons, and their urine less toxic than normal.

It has often been stated that the eclamptic blood is more toxic than the blood in normal pregnancy. Lash and Welker tested the action of blood serum proteins in normal pregnancy and in eclampsia, by injecting large doses intraperitoneally into animals, but they could find no evidence of increased toxicity of the blood serum proteins in the latter.

In general, there are two types of toxins that may produce toxic symptoms; first, those substances which are usually present in the body in definite proportions and which in the disease appear in increased or decreased concentration. To this group belong such body constituents as sodium, calcium, potassium, magnesium, etc. (2) The poison concerned may be a substance foreign to the body, and to this group would belong such substances as the split products of the proteins, for example: tyramine, histamine and ergotamine.

b. Foetal elements. In 1902, Veit advanced the theory that fragments of chorionic villi and foetal ectoderm entered the maternal circulation and acted as a poison which he called syncytio-toxin. This he supposed is normally neutralized by an anti-body called syncytiolysin, but when the former is in excess of the latter, eclampsia develops. He based this hypothesis on the fact that foetal ectoderm and fragments of chorionic villi are constantly entering the maternal circulation, and believed that he had proved his theory when he found that an emulsion of human placenta injected into the peritoneal cavity of rabbits caused death of the animal, which showed albuminuria.

Hull and Rohdenberg in 1914 suggested that when an excess of

foetal elements is thrown into the maternal circulation, it is autolyzed with the formation of an excess of leucin, which in turn injures the hepatic vessels with resulting thrombosis, cloudy swelling, necrosis and even autolysis of the liver cells. They also considered that the renal changes in eclampsia were probably due in part to other products of autolysis.

c. Foetal metabolic products. Fehling and Dienst advanced the theory that products of foetal metabolism cause eclampsia. The well known fact that death of the foetus in utero, or delivery, often results in cure of the disease, made it quite natural to suppose that eclampsia may be foetal in origin. The occurrence of intercurrent eclampsia, in which complete cure occurs without delivery, speaks against this theory. It is generally believed that the death of the foetus in utero during eclampsia is followed by cure, but Maurice and Powilewicz in studying 94 cases found that in only 23 cases did the toxemia clear up after the death of the foetus. In contrast to this, they observed that in patients who gave birth to living children, the toxemic symptoms disappeared shortly after delivery. Seitz states the foetus causes the intoxication of eclampsia; while Hirst believes that the toxins of eclampsia originate mainly in the foetus and to a lesser extent in the placenta. Novak writes that the poison comes from incomplete and decomposed substances which are not completely excreted, in other words, a metabolic poison.

Certain investigators believe that because eclampsia can occur in cases of hydatidiform mole, the foetus can be ruled out as its cause. Frey described the case of a primipara, apparently six months pregnant, who from the fourth month onward had shown albumin in the urine. She had some bloody discharge and five convulsions before admission to the hospital. A cesarean section was performed, a hydatidiform mole removed, and the patient recovered. Similar cases have been reported by Folk, Olshausen, Hitschmann, Kroemer, Dienst and Sitzenfrey, and Gross. Frey suggests that the real cause of eclampsia is probably not the poison from the waste products of the foetus, but that the disease is due to a disturbed function and an internal secretion of the placenta itself. Wigger in 1928 reported the eighth case of eclampsia occurring in conjunction with hydatidiform mole, and holds that the foetus can be ruled out as the cause, but not the placenta,

as one still has chorionic epithelium in a mole. Consequently he does not agree with those who regard the occurrence of eclampsia in hydatidiform mole as an argument against its placental origin.

d. Placenta. Cheinisse states that the theory most generally accepted at the end of the nineteenth century, attributed eclampsia to the presence in the blood stream of a toxin coming from the placenta.

Since that time numerous experiments on the placenta and on placental extract have been conducted with the hope of finding the causal factor. Young has for many years claimed that the toxemias of pregnancy are especially associated with infarction of the placenta, and has developed his theory of placental autolysis to explain the etiology of eclampsia. Moreoever Young and Miller state that the placental degeneration is due to interference with its blood supply and that absorption of the placental poisons occurs through portions of the placenta attached to the uterine wall. They further reason that the toxemia may be associated with placenta praevia or premature separation of the placenta. Symptoms of eclampsia, they believe, are due to the absorption of broken down liver cells and possibly other cells, which are killed by the poison coming from the placenta. In cases of eclampsia where there is no placental infarction, they think the changes in the placenta are so minute that they cannot be detected by the microscope, but nevertheless give rise to sufficient toxin to cause the disease.

Several authors have studied the relationship of placental infarcts to eclampsia, but have failed to detect any definite connection. Williams believes that placental infarcts when present in cases of eclampsia should be regarded as accidental findings, or at least as secondary to the toxemic condition, and not as its cause as Young believes.

In 1901 Cocchi had produced lesions in the kidneys and liver, by injection of a placental substance. Since then placental hormones have been described, and the Abderhalden reaction has been developed. Bory, reviewing the work on placental toxins, concludes that physiologic syncytiolysis is the fundamental process in the causation of eclampsia. The presence in the blood stream of a substance which can activate the placental enzyme or toxin, and the absence of some inactivating substance, which normally protects the organism, he regards as secondary factors.

Gessner states that the occurrence of eclampsia associated with hydatidiform mole made it possible for Veit to develop his placental theory, but he argues that since the human race is the only one in which eclampsia occurs, although there are many other animals with a placental circulation similar to that of women, we are not justified in concluding that the disease is caused by a poison from the placenta. Moreover in certain conditions large quantities of placental ferment may be thrown into the blood stream without the development of eclampsia. In chronic nephritis, for example, there is usually abundant infarct formation in the placenta and yet eclampsia is a rare complication of that condition.

Selitzky considers that the toxemias are caused by unknown toxins coming from the endocrine glands and particularly from the internal secretion of the placenta, or from a functional modification of ovarian secretion.

Ishikawa made an alcoholic extract of the placenta of the rabbit and tested its toxicity. He came to the conclusion that an injection of such an extract, as well as of the foetus, produces anti-bodies in the rabbit and that proteins favor their formation. Oettingen and Schwoerer take issue with Obata, who holds that eclampsia is nothing but an intoxication from a placental poison. These authors do not believe in a specific placental toxin, but consider that eclampsia is due to the action of a by-product of metabolism.

In a series of experiments on artificial placental circulation, Dellepaine showed that the placental tissue possesses proteo-clastic properties which break down complex nitrogenous molecules into amino-acids, and that when large amounts of them are present the placenta causes their disappearance. He found no corresponding increase in ammonia and therefore reasoned that the amino-acids were elaborated synthetically. From his experiments he further concluded that the placenta manifests slight ammonio-genetic, as well as ureo-genetic activity. Zweifel found that the injection of foetal and placental albumin from one animal into another, of the same species, did not cause a hypersensitiveness as one would expect in the development of anaphylaxis, and consequently concludes that eclampsia is not due to such a reaction.

Stern, Lokchina and Falk tested the permeability of the placenta in

rabbits and rats and noted that colloids do not pass from the placenta to the foetuses. The crystalloids similarly do not pass through, except in very early pregnancy. They also noted that inhalation of carbon-monoxide so changed the permeability of the placenta that crystalloids would pass through it, while colloids were held back. Soli suggests that there is a possibility of the direct escape of foetal blood into the maternal circulation, because in eclampsia he noted an alteration in the villous capillaries, with diminished resistance of their walls. For this reason he holds that eclampsia is probably an anaphylactic reaction. Aranjo, on the other hand, regards the placenta as a protective mechanism both to the mother and to the foetus. It has a glycogenetic function, like a sort of uterine liver, which decreases during the later months of pregnancy when the foetus can take care of its own carbohydrate metabolism. The passage of undecomposed fat is impossible. He does not believe in a placental poison itself, but thinks that in certain cases the placenta may be insufficient and therefore fail to act as a protection to the mother, and that this insufficiency may be raised by the injection of placental extracts. Chappaz also regards the placenta as something more than a mere passive filter, and considers it as an actual regulating mechanism determining what substances shall pass between mother and child. Moreover, it seems well established from the work of Slemons and Stander, Tyler and Underhill, Mendel and Daniels, Wesson, and others that the placenta is impenetrable to fats and lipoids. Amino-acids and carbohydrates, on the other hand, pass from mother and child, and from this it would appear that the placenta acts simply as a semipermeable membrane.

e. Infectious theory. The bacterial origin of eclampsia was suggested in 1884 by Delore and Rodet, and since that time numerous writers have reported the finding of various bacteria in the urine and blood of women suffering from eclampsia. At present, however, no one seriously believes that there is any basis for regarding eclampsia as due to any specific bacterium.

Talbot believes that the toxemias of pregnancy are always associated with focal infection, and holds on the basis of clinicial observation that bacteremia, pyaemia and retro-placental abscess are frequently associated with the toxemias. Ivens is also a firm believer in the infectious origin, and recently Keller further expanded this theory and

gave the detailed account of eleven cases of eclampsia in which the urine showed bacterial growth. He states further that "with all the various theories of eclampsia and the site of its origin, the only organ which is constantly involved is the kidney. In 289 cases observed there were kidney symptoms in every one and pathological changes in all that went to autopsy. DeLee states the theory that eclampsia is due to an intoxication, is a toxemia, is most generally accepted, while it is admitted that the source and nature of the poisons are unknown. If we knew whether the toxemia came from the liver, the foetus, the placenta, the intestines, the general metabolism, disturbed glandular balance, from bacterial activity or from any other source, it would help our treatment immensely, but as yet we are groping blindly, empirically. However up to the present time no one has been able to isolate a germ that could be called causative."

Loomis writes that it is reasonable to assume that irritation from chronic sepsis may be a factor in lowering kidney and liver function and so play a rôle in the production of eclampsia. He lays special stress on dental abscess as a possible source of chronic sepsis, and although he does not believe that the dental abscess is the cause of toxemia, it may readily play a very important rôle.

f. Endocrines. During pregnancy the thyroid gland hypertrophies, and there is also evidence of anatomical changes in some of the other endocrine glands. Many attempts have been made to associate eclampsia with one or other endocrine disturbance. Lang, Ward and others suggested that failure to hypertrophy on the part of the thyroid gland may lead to toxemia of pregnancy. Today there is no convincing proof that the thyroid is of etiological significance in the production of eclampsia, and the same may be said regarding the parathyroid, as will be seen under the discussion on calcium metabolism.

Williams and Wallis hold that hyperactivity of the corpus luteum is the cause of eclampsia. In both menstruation and pregnancy this hyperactivity stimulates the thyroid gland to increased activity. Sometimes there is overproduction of this substance, when it escapes into the blood stream, and according to them causes vomiting of pregnancy or eclampsia. These authors state that the presence of an excess of cholesterol in the blood in pregnancy is very significant, as it occurs about the fourth month and at the time when the corpus

luteum is most active. In eclampsia the hypercholesterolemia is more marked than in normal pregnancy, and it has been shown that injections of corpus luteum extract increase the cholesterin content of the blood. They regard the increased cholesterol content of the blood as an attempt by the body to neutralize the toxic substance which comes from the corpus luteum. They experimented on rabbits with extracts from fresh corpora lutea of the pig and the human being, and were careful that the solution contained no cholesterol, cholin, histamine, tyramine, or protein. Such extracts injected into animals produced lesions similar to those found in the kidneys of women dying from eclampsia; but, in view of the fact that we have already stated that the renal lesions in eclampsia are very variable in extent and probably entirely secondary in character, their arguments do not appear very weighty. They conclude that the corpus luteum contains a chemical compound which can produce necrosis in animals as well as other changes similar to those encountered in eclampsia; and that an overproduction of this particular substance is the cause of eclampsia. They were not able to find such a substance in the placenta or in hydatidiform mole.

Hofbauer advocated the view that hyperfunction of the hypophysis and adrenals, resulting from insufficient secretion of the ovaries, caused eclampsia. Küstner in testing the various sera as to their action on pituitrin, comes to the conclusion that while normal non-pregnant serum has no effect on the action of pituitrin, pregnant and parturient serum has a supporting but not an inhibiting action, while the serum during the puerperium has no supporting action, and contains substances that soon produce disintegration of the pituitary principle. The serum from women with eclampsia has a supporting action and only a small inhibitory action. From these results, the author concludes that eclampsia is caused by a hypersecretion of the posterior-pituitary lobe hormone, or by a deficiency in the antibodies for this hormone and perhaps for the hormones of the other endocrines. In more recent work on this subject, this author found that there are three substances in the blood which effect the action of pituitary substance; these are: no. 1 which helps the action of pituitary, no. 2 which inhibits the action of pituitary, and no. 3 which completely neutralizes the action of pituitary principle. His conclusions are that while in normal

pregnant serum there is a considerable amount of no 1, none of no. 2, and a slight amount of no. 3, in eclampsia, on the contrary, there is a very great amount of no. 1, and a small amount of no. 3. He thinks that the toxin causing eclampsia acts on the vessel walls, since the most important finding of eclampsia is hypertension, and that the toxin probably comes from a dysfunction of the endocrine glands, and most probably from a hyperfunction of the hypophysis.

It may be interesting to learn in this connection that eclampsia has been reported following the use of pituitrin. Van Cauwenberghe observed an outbreak of eclampsia seventeen hours after delivery in a multipara who previously had no albumin in the urine, but who had received an injection of pituitary extract at the end of labor. Weymeersch has also reported the eclamptic attacks becoming more frequent and more violent after using pituitary extract. But, as pituitary extract is routinely used after the third stage of labor in many clinics, without any appreciable increase in the incidence of eclampsia, such observations must be regarded as purely coincidental.

Kark discusses a possible analogy between acromegaly and eclampsia, and regards the latter condition as essentially an overfunction of a physiological process.

g. Biological reactions. Schmorl, Veit, Lubarsch, Williams and others have drawn our attention to the fact that throughout the entire period of pregnancy, placental or foetal cells enter the circulation of the mother, a fact which has led to two further theories concerning the causation of eclampsia. The first depends upon agglutination and hemolysis, and the second upon an anaphylactic reaction.

Dienst in 1905, tried to show that foetal cells invaded the maternal organism, and produced changes in agglutination in the blood. McQuarrie studied the question of iso-agglutination and found that the toxemias of pregnancy occurred far more frequently when the maternal and foetal bloods were incompatible. Allen, in a much larger series of cases, could not corroborate the findings of McQuarrie, and holds that while interagglutination might possibly explain the occurrence of eclampsia in general, as well as its greater frequency in multiple pregnancy, it seems difficult to understand its relationship to the greatly increased incidence of the disease in primiparae. Moreover, the interagglutination theory cannot explain the occurrence of eclamp-

sia with hydatidiform mole, since in the majority of instances the degenerated villi contain no foetal blood. Allen studied the iso-agglutination characteristics of the blood of 375 normal and 104 toxemic women and their new born children. He found no evidence that incompatibility is more frequent in toxemic than in normal pregnancy, as is indicated by the fact that it was demonstrated in 20.8 per cent of the normal, and in 21.1 per cent of the toxemic pregnancies. Likewise he could find no evidence of specific immunization of the mother against foetal corpuscles.

Gruhzit, on the other hand, found that in the majority of cases of eclampsia, foetal and maternal bloods were incompatible, and he further observed that the blood of the eclamptic had a high viscosity, which he believes is due to the passage of incompatible blood elements from the foetus into the maternal blood stream. This author further reasons that the high viscosity of the blood in eclampsia brings about a colloidal condition which can produce congestion, stasis and oedema, and which in turn brings about lowered body function. As a result of this lowered metabolism, the hydrolysis of proteins and the oxidation of carbohydrates are slowed down, resulting in an acidosis. High blood pressure is also a result of this new colloidal condition of the blood. Jarzew has also claimed that the increased viscosity of the blood is an important factor in the production of eclampsia.

Louros believes that a primary dilatation of the uterine vessels may cause an increased blood pressure in the periphery. He, therefore, regards the constriction of peripheral blood vessels in pregnancy as secondary to dilatation of the abdominal vessels, caused by stimulation of the vagus. In other words, we have to deal with a vagotonia. Louros and Schmechel produced dilatation of the blood vessels in the region of the uterus in rabbits, and then ligated the hepatic vein, with the results that eclamptic-like changes developed in the liver. Louros thinks there are two types of eclampsia. In the first type there is vagal stimulation from an anaphylactic condition, which is gradually produced and compensated for; while in the second type the compensation does not take place, resulting in a falling blood pressure. He calls this second type the anaphylactic form. He holds that the vagal stimulation is caused by a disturbance in the general metabolism, which starts in the foetus, and that a vicious cycle exists between

metabolism and the vegetative nervous system. Moreover, he believes that constitutional factors are of importance, because women subject to vagal changes are prone to eclampsia.

The anaphylactic theory was proposed by Rosenau and Anderson. The principle of this hypothesis is that foetal protein enters the maternal circulation and under certain conditions may cause an anaphylactic reaction, very similar to that seen in other well-recognized forms of anaphylaxis.

Levy-Solal and Tzanck produced death in animals by the injection of sera of eclamptic women. From these sera they isolated two active principles, an anaphylactic principle causing convulsions, and a toxic one which was less severe in action, the anaphylactic principle, belonging to the class of antigens. Levy-Solal described three types of eclampsia, kidney eclampsia, liver eclampsia, and anaphylactic eclampsia. He believes that there are many cases in which neither the kidneys nor the liver are involved, and these he believes may possibly be associated with disturbances of the endocrine glands. Lawrence likewise states that eclampsia is an anaphylactic reaction, and that the convulsions follow failure of antibody production. In support of his contention, he mentions the favorable results following attempts to raise the antibody production and to decrease the amount of foreign protein in the system. According to him, colonic irrigation, gastric lavage and morphine increase antibody production, while foetal death, delivery or venesection may control the convulsions by checking the production of foetal toxins.

h. Mammary. Sellheim suggested that the toxic substance causing eclampsia is elaborated by the mammary gland and that the disease is analogous with parturient paresis in cows. Indeed, he carried his belief so far as to amputate the breasts from a patient suffering from severe eclampsia. Shortly thereafter, Healy and Kastle announced a similar belief and stated that they could produce eclampsia experimentally by injecting into guinea pigs small quantities of colostrum from cows suffering from parturient paresis, and they even found liver and kidney lesions in their animals suggesting eclampsia. Williams is skeptical about their results. Wilson stated that there are the following differences between the two diseases: (1) parturient paresis rarely attacks primiparous animals, while eclampsia is particularly

common in primiparae, (2) parturient paresis occurs almost entirely postpartum, while eclampsia occurs antepartum, intrapartum and postpartum, (3) parturient paresis increases in frequency in direct ratio with the rate of milk production, while this is not true in eclampsia, and (4) there is a glycosuria in parturient paresis but not in eclampsia. Harding, Murphy and Downs in a manuscript sent to the author, and which will be published shortly, give an excellent review of the subject, and state that since the work of Wilson the mammary theory has fallen into disfavor, although there are still some investigators who believe that it may prove of assistance. Schmidt in 1897, showed that by the injection of a small amount of potassium iodide into the udder the mortality in parturient paresis may be greatly reduced, and the present practice of inflating the udder with air has almost entirely done away with the mortality of the disease. Greig and Browne have recently been experimenting to find a simple means of inflating the human breast, although Harding and his co-workers conclude that it is unlikely that eclampsia in women is analogous to parturient paresis in cattle.

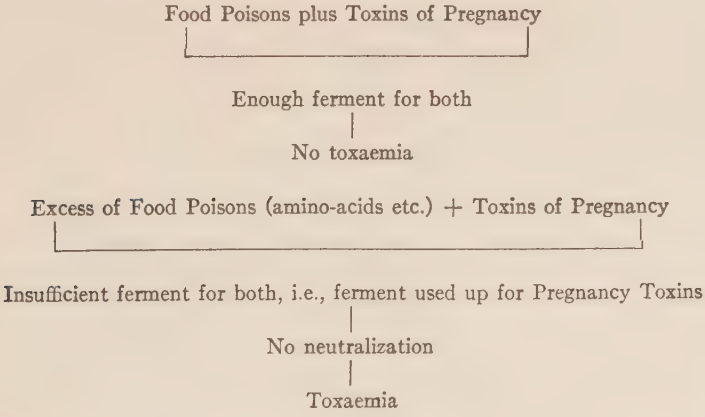
Pierrson on the other hand believes that the two diseases have so much in common, that it may be assumed that the same etiological factor underlies both. He believes that this consists in an over abundance of foetal nourishment in the maternal blood, and further suggests that repeated expression of the colostrum from the mammary glands might act as a prophylactic measure.

i. Diet. Diet has many times been under suspicion as the cause of eclampsia. Tweedy in 1913 suggested that ordinary food becomes poisonous during pregnancy and may give rise to eclampsia. He was led to this belief by the fact that women who partake of food, even in small quantities, often had a recurrence of the convulsions. Tweedy reasons that the antibodies in whole blood not only guard against bacteria, but also against products of digestion which may have entered the blood stream. He holds that the antibodies are stimulated by an antigen, which is present in colostrum, and that they have to hyperfunction, as it were, during pregnancy, as they are called upon to neutralize the foreign protein which gains access to the maternal blood stream from the ovum. Tweedy thinks that correctness of such a view is proven by the Abderhalden tests. Should the maternal

antibodies be unable to handle the food particles coming from the diet, as well as the protein coming from the foetus, the result may be serious and the patient develop eclampsia. He explains postpartum eclampsia on the theory that the mother's intestine contained food at the time when the convulsion developed.

Sellheim writes that eclampsia is more common in those who live on an animal diet, than in vegetarians. Reference has already been made to the fact that during the war the incidence of eclampsia fell, and this was attributed to the lack of protein and fat in the diet. Ruiz-Contreras argues that since eclampsia occurs less frequently among the poor than in well-to-do patients, and since the incidence was less during the war, when there was a shortage of food, particularly in meat and eggs, the cause of eclampsia must be sought in the diet.

In a personal communication Bethel-Solmons, regarding the etiology of eclampsia writes as follows: "We know that certain foodstuffs disagree with certain people, though they are perfectly harmless to others. Even the capacity of an individual to assimilate a certain food, changes, so that a food, which at one time may be taken with impunity, at another time acts as a virulent poison. Such changes are not uncommon in pregnant women. It is well known that all foreign proteins must be changed by the ferments of the body before they can be assimilated, and if they are absorbed without undergoing such change, they act instantly as most virulent poisons. Eclampsia may be explained in this way.



"On entering the body, this tox-albumin must be neutralized by the ferments (anti-bodies) already present, if its destructive effect is to be avoided.

"It is reasonable to conclude that the ferments which effect this neutralization are those which fix the amino-acids derived from food. These acids are not inexhaustible, as proved by the sickness and exhaustion which may follow the ingestion of certain food, such as eggs and lobsters. Similarly, we may suppose that the ferments are used up in the effort to counter the placental toxin; and the blood in this exhausted state can no longer deal effectively with additional food particles, the derivatives of which will now act as an irritant poison, destroying either directly or indirectly, the liver and kidney cells, and bringing on the well known symptoms of eclampsia. It must not be forgotten that the irritant poison present in the blood at this stage cannot be eliminated until its corpuscles get broken up into some less harmful product, such as urea. The absorption of these foreign proteins in this unprepared state, is the determining factor in eclampsia. This seems to us a complete explanation, which is controverted by no known clinical fact, and further, is certainly much more fruitful for purposes of treatment than any that has previously been put forward.

"Our views may be summed up by the following tables which show that if toxin enters the blood stream by chorionic villi in blood sinuses or from placental infarcts, and accompanied by excess of food, toxaemia results."

j. Renal origin. Volhard who has done a great deal of work on the various forms of nephritis, regards eclampsia as a form of acute uremia, and has proposed the term "eclamptic uremia." He believes that the convulsions may arise independently of the kidney function, and are due to general vaso-constriction, which is evidenced by the increase in blood pressure, which leads to ischaemia and oedema of the brain.

Paramore holds that the kidneys are always implicated in eclampsia, and that the convulsions are preceded by renal dysfunction. A diminished output of urine is a constant finding in the pre-eclamptic state, but he further reasons since women with chronic nephritis rarely develop eclampsia, that eclampsia must depend upon some other factor than inefficient kidneys, and that this may be found in an inefficient liver. Paramore believes that eclampsia is simply an uremia, in others words a pathological state characterized by a rise of nitrogenous waste or by-product in the blood, due to impairment of the liver or kidneys, or both. He is convinced that as the result of the rapid enlargement

of the uterus the intra-abdominal pressure is increased in pregnancy and more especially in primiparae, and he holds that the incidence of eclampsia is in relationship with this increased abdominal pressure.

Fitzgibbon believes that the pathological findings in eclampsia and other forms of toxemias of pregnancy are identical and that a subacute nephritis is present in all cases. The cause of the toxemia or eclampsia is an extra demand on the organs of elimination and the failure of these organs to keep pace with the excretory demand. Casamada, on the other hand, writes in 1928, that there is no association between eclampsia and kidney toxemias.

Poten in a recent article states that eclampsia is primarily due to renal insufficiency, and this is in turn due to dilatation of the ureters. He has devised a treatment which consists in performing a temporary ventral suspension of the uterus after delivery in order to avoid pressure on the ureters. He does not believe that eclampsia is caused by a placental poisoning, because of the fact that we very seldom, if ever, see eclampsia in the child, although the placenta is common to both circulations

k. Oedema theory. The hypothesis that oedema and actual anemia of the brain are the etiological factors in the production of eclampsia was first proposed by Traube and Rosenstein, in 1864. Straus and Widal think that salt retention causes oedema, and it is on this basis that Zangemeister has developed his theory that ecalmpsia is caused by oedema of the brain, and that in this disease the actual poison is water. He believes that the blood vessels become more permeable during pregnancy, so that water accumulates in the tissues with the result that the extra-vascular pressure increases, and that the intravascular pressure does not rise proportionately. With the increasing extra-vascular pressure there will be produced in the brain, decreased blood supply. This decreased blood supply means insufficient oxygen and imperfect nutrition of the brain cells, so that anaemic areas result. The process goes still further until areas of necrosis actually develop. Somewhere in the development of the latter, there will be an irritative stage in which the brain cells fail to receive the proper nutrition, and these "irritative" areas cause tonic and clonic muscular contractions.

Zangemeister thinks that at an early stage in this sequence of events water accumulates in the tissues, resulting in an abnormal increase in

the body weight. He consequently lays great stress on watching the increase of weight during gestation, and whenever it is much in excess of the normal limits, regards it as a danger signal. Damaged kidneys may play a part in the diminished output of urine and thus further accentuate the increase in body weight. It is interesting to note that all authors consider a certain degree of oedema as an almost universal accompaniment of pregnancy. Thus, Fink found it to some degree in 95 per cent of a series of 350 patients. He does not regard this as due so much to disturbed kidney function, as to an abnormal balance of the activity of the cells, as far as water metabolism is concerned. He thinks that this abnormal cell reaction to water may be associated with the action of various hormones and internal secretions which are presumably increased during pregnancy.

Wieloch made a study of 213 patients in order to determine the rôle of oedema in the causation of eclampsia. He believes that the primary cause of oedema is injury to the capillary endothelium. According to Zangemeister the increase in the blood pressure is of extra renal origin and is due to stimulation of the vasomotor centers through increased cerebral pressure, the latter in turn resulting from oedema of the brain. Wieloch concludes that the cerebral pressure theory explains the convulsons, as well as the headache, vomiting and fever.

l. Capillary spasm. Haselhorst examined the capillaries in normal non-pregnant, as well as in normal and abnormal pregnant women, and found that in eclampsia they are widened and lengthened, and that the blood corpuscles circulate through the capillaries in an irregular way with frequent periods of stasis. He has also demonstrated these changes by means of microphotographs taken three to ten weeks after delivery, and has also observed the occurrence of spasm in the capillaries of the eye during eclampsia.

Hinselmann, Nevermann, and Heynemann have made similar studies of the capillaries in eclampsia and have confirmed his results. Haselhorst believes that the spasm of the capillaries is the result of disturbance of the vascular nervous system, and is not due to an organic change in the vessel itself. Heynemann is also a firm believer in spasm of the vessels, but does not think that their cause has been definitely established.

Waschetko and Seletzky made studies on rabbits before and after

irritation of the cerebral cortex by means of an electric current. After the experiment had been repeated several times on the same animal at intervals of less than three days, they found that a small electric charge is required to cause convulsions; in other words, the cerebral cortex is labile to the electric stimulation. On the other hand, if the animal is allowed to rest for seven or more days after the experiment, as great a charge is required to bring about convulsions as at the first experiment.

m. Oxygen deficiency. Halbertsma believes that a deficiency of oxygen is the immediate cause of eclampsia; Rodenaker also regards a disturbance of oxidation as the exciting cause, and holds that the oxidizing power of tissues normally decreases towards the end of pregnancy and that in eclampsia it falls far below the normal level.

Hochenbichler regards eclampsia as an acidosis, due to lack of oxygen, and has demonstrated that a lowered bicarbonate reserve in the blood can be raised after exposure to ultra-violet light. He therefore recommends its use in treating eclampsia. Stander, in discussing the significance of the increased lactic acid of the blood in eclampsia, stated that whatever theory ultimately explains the etiology of eclampsia will have to take decreased or deficient oxidation into account. He considers this phenomenon as the most fundamental finding yet discovered in eclampsia.

n. Nervous origin. Elwyn has suggested a new explanation for the cause of eclampsia, which is based on his belief that there are two neuro-muscular mechanisms; one regulating vaso-constriction, and the other the contraction of the uterus. Both mechanisms are controlled from the midbrain and the impulses from these high centers travel by way of the thoracicolumbar outflow of the sympathetic nervous system. He believes that with the progress of pregnancy the irritability of the whole neuro-muscular mechanism for uterine contraction has become increased, and because of the proximity of the two centers, the increased irritability spreads to the center for vaso-constriction. This then leads to an increased irritability of the entire neuro-muscular mechanism of the arterial system, so that the arteries pass into a state of tonic contraction. As a result general arterial spasm develops and may lead to eclampsia. He regards this theory as particularly fitted to explain the mode of production of postpartum eclampsia.

Other theories, based on the effect the amniotic fluid may exert, on changes in the size of the protein particles, or on even more phenomenal changes, have been suggested, but unaccompanied by sufficient experimental or clinical data to warrant discussion in this paper.

o. Liver in eclampsia. At the end of the eighteenth century, Jurgens demonstrated that eclampsia was associated with liver changes, following which Pinard developed a theory that liver changes were associated with the etiology of the disease, "hepatotoxemie gravidique." The French authors of that time also spoke of "Insuffisance hepatique." Hofbauer in 1907 described what he thought was a typical liver of pregnancy, characterized by fat infiltration in the cells in the central part of the lobule, disappearance of glycogen, and dilatation of the bile channels, central vein and afferent capillaries, and consequently believed that it was normally in a state of diminished resistance. However, several later investigators failed to confirm Hofbauer's findings (Schickele and Heinreichsdorf). Opitz and Heinemann found that there is frequently an abnormal deposit of fat in the liver and on this basis it may be justifiable in speaking of a liver of pregnancy. Schickele has also shown fatty infiltration in the liver of pregnant animals. According to Basilevie and Jancenko, there is a disturbance of liver function in pregnancy, as shown by a decrease in the surface tension of the urine.

During the past ten years a great deal of work has been done on methods to determine hepatic function. Saitz studied the liver function in 25 normal pregnant women and observed that the excretion of uric acid is increased in 84 per cent, and ammonia and amino acids increased in 88 per cent. Bilirubin was increased in the blood in 8 per cent of the patients, while urobilin was increased in the urine in 64 per cent. He also noted an increase in cholesterol in the blood as well as a change in the carbohydrate metabolism as shown by the fact that a longer period is required for the assimilation of levulose, than in normal non-pregnant women. He does not know whether the changes are due to the liver, and concludes that one is not justified in definitely recognizing such an entity as the "liver of pregnancy." Kolmer, on the contrary, after examining a large series of livers microscopically, is convinced that there is such an entity. The phenoltetrachlorphthalein test developed by Rosenthal, has been used by many investi-

gators. In the toxemias of pregnancy, Smith found that retention of the dye occurs in eclampsia and pre-eclampsia, but that its degree does not appear to be an index of the amount of liver damage. Siegel substituted bromsulphthalein for the phenoltetrachlorphthalein test and believed that by its use he was able to differentiate between eclamptic and nephritic toxemias as he thinks that it gives valuable information regarding the amount of liver impairment. Schneiders and Rosenfield also feel that such liver function tests are of value in determining the amount of liver damage in the toxemias of pregnancy.

Piersol and Bockus found that the phenoltetrachlorphthalein liver function test gave fairly accurate information regarding liver damage, and whenever the excretion of the dye was delayed, they found urobilin in the urine. Naujaks also found that in the presence of liver injury there is always a delay in the excretion of the dye, but in the toxemias of pregnancy he was unable to find any parallelism between the severity of the disease and the result of the test. Krebs and Dieckmann also used the Rosenthal test but are not willing to draw any definite conclusions as to its prognostic value in toxemia, but are inclined to believe that it may afford an index as to the amount of liver damage in cases ot toxemia. King, reviewing the different liver function tests, states that the phenoltetrachlorphthalein, as well as its successor, the bromsulphthalein test, is of definite value, and that the degree of retention of dye seems to correspond with the severity of the toxemia. The van den Bergh test he found to be negative in pre-eclampsia and eclampsia, and he agrees with Piersol and Bockus that the Widal hemoclastic crisis test is of little value in toxemia of pregnancy. Eufinger and Bader disagree with King that the van den Bergh test is of little help in eclampsia. Their experiments showed that it reveals marked damage to the liver in the vomiting of pregnancy as well as in eclampsia. Steen also emphasizes its importance, as it makes possible the demonstration of hyperbilirubinemia at a time when it cannot be detected by any other means.

Herold used the method of Heilmeyer to test the pigment formation in the urine, in order to establish whether there is impaired liver function. In eclampsia he found a definite degree of liver damage, and is convinced that it is very slowly repaired as it is only late in the puerperium that the value of pigment substances is restored to normal.

Certain of the liver function tests have been tried in this clinic, and judging from the results obtained, as well as from the above account of the work of others, the author has come to the conclusion that very rarely do we gain information sufficiently important to warrant the institution of a routine liver test in patients suffering from toxemia of pregnancy. The chemical analysis of urine and blood, as we shall shortly see, invariably reveals the absence or presence of liver damage. Consequently, we have, perhaps somewhat prematurely, relegated liver function tests to the same class as the phenolsulphenophthalein test of kidney function in pregnancy toxemia.

Bile is composed of three main constituents: bile salts, cholesterol and bilirubin. According to Mann it seems that bile acids are made in the liver, though this has not been proven. We know very little about cholesterol metabolism. The other function of the liver is that of helping in protein metabolism and especially with reference to the purine bodies. Urea and uric acid are important nitrogenous by-products. Mann's experiments also prove that the liver is the main organ concerned in the destruction of uric acid. Among the unsolved problems, so far as the liver is concerned, is the part which it plays in fat metabolism. It is supposed to help in the transformation of fat into carbohydrate, although this has not been proven.

Mikeladse showed that in the toxemias of pregnancy there is an extreme degree of bilirubinemia. Saitz, Heynemann, Eufinger and Bader, Hermann and Kronfeld, Bakscht and Mikeladse, all regard the degree of bilirubinemia as of great diagnostic and prognostic value in toxemias of pregnancy. Mandelbaum, on the other hand, found that there is no relationship between the amount present in the serum and the degree of toxicity.

From the above it seems fairly well established that liver damage is one of the most constant findings in eclampsia. Whether this hepatic injury is "post hoc" or "propter hoc" is not yet known, although the author is inclined to believe that it appears very early in the development of the disease. Theories as to the agents responsible for such injury will be discussed under the following heading.

Chemical changes in eclampsia. From the account just given of the various theories concerning the etiology of eclampsia, it must be clear that no hypothesis, so far suggested, is accompanied by sufficient

evidence or experimental proof to be considered conclusive. We have seen in the earlier part of this review what marked maternal metabolic changes are always associated with normal pregnancy, and it is therefore natural to suppose that similar disturbances may play a rôle in the development of eclampsia. Consequently, in order to study this question, it becomes imperative to know how the mother's blood, urine and general metabolism are affected when she suffers from this disease.

A great deal of work has been done on the chemical findings in the urine and blood of eclamptic patients. Zweifel, in 1904, showed that in the urine the urea-nitrogen is lowered and the ammonia nitrogen raised. Stookey also found a low urea nitrogen (70 to 83 per cent of the total nitrogen) and a high ammonia nitrogen (5 to 10 per cent of the total nitrogen) in the urine as well as a high mono-amino-acid nitrogen and a positive para-dimethylaminobenzaldehyde reaction.

Hynd determined the optical activity of the urine in eclampsia and found it to be considerably less laevorotary than one would expect from the amount of protein shown. In 14 cases of eclampsia he noted that the protein in the urine was of two groups—one similar to serum albumin and the other approximately resembling cow's albumin, and concludes that in certain types of eclampsia it may be mainly lact-albumin, which affords a certain plausibility for assuming that eclampsia may be an anaphylactic reaction due to a foreign protein in the blood stream, or possibly, that the mammary glands may be an important factor in its causation.

Without reviewing in detail all the investigations on the composition of the urine, it may be stated that thus far no other marked disturbance has been noted in the eclamptic urine, with the exception of this shifting in the nitrogen partition, plus a decreased chloride excretion and an acetonuria. The pH of the urine has not been carefully studied in eclamptic patients. Zinsser made a biological study of the toxicity of the urine obtained from 9 cases of eclampsia. Upon injecting it into the peritoneal cavity or the circulation of guinea pigs, he found, contrary to the results of Pfeiffer, that death did not follow and so he concluded that there is nothing to warrant the assumption that a disintegration of albumin causes eclampsia, although Pfeiffer had stated that a discharge of albuminoids may produce an anaphylactic reaction.

p. Nitrogenous retention. More information, which may lead to an understanding of the etiology of the disease, has been accumulated on the chemical changes of the blood. It is generally agreed that the non-protein nitrogen of the blood is not increased in eclampsia. Where we do find a high non-protein nitrogen it is usually late in the disease and as a result of injury to the kidneys produced by the eclampsia, or of some factor dependent on the attack, as will be seen later. The same may be said with regard to the blood urea. J. T. Williams, in 1921, directed our attention to the fact that uric acid is definitely raised, and quite early in the course of the disease.

His findings have been abundantly confirmed by Caldwell and Lyle, Killian and Sherwin, King and Denis, and Stander. Hardy, Allin and Eagles showed that the blood uric acid was invariably raised when the patient was on a high fat diet and indicated that the change might be explained on the basis of decreased excretion. On the other hand, Cathcart, Graham and Poulton, and Umeda had all noticed a decreased excretion of uric acid in high fat diets.

Creatinine is the anhydride of creatine and a constituent of normal human urine. Very little is known regarding the excretion in eclampsia. The changes in the blood creatinine seem to depend entirely on the kidneys, and from the work of Mann and his associates it would appear that the liver does not play an important rôle in the creatin-creatinine metabolism. No outstanding disturbance in creatinine or creatine metabolism has been noted in eclampsia.

q. Inorganic constituents of the blood. Parathyroid tetany is always associated with a marked lowering of the blood calcium, and it is perhaps for this reason and because of the occurrence of convulsions in the two conditions, that so many attempts have been made to establish a connection between low blood calcium and eclampsia. Only the more recent contributions on this subject will be reviewed in this paper.

Calcium deprivation of the mother, resulting from the drain on her supply by the foetus, has furnished a wide field for speculation. As shown in the earlier part of this paper, the blood calcium is slightly lowered during the latter third of pregnancy, being at about the lower limit of normal.

Deschamps found the non-pregnant values to average 11.4 mgm.

per 100 cc. of blood, with limits of 10.4 and 11.5; in pregnancy from the second to the seventh month 10.6 to 11.97; at the eighth month 10.6 to 13.90; and during the ninth month 10.16 to 14 mgm. In eclampsia, the lowest figure recorded by this author was 9.4. Lemers likewise found a decrease in the blood calcium value in four cases of eclampsia. But on the other hand, Denis and King, as well as Stander, Duncan and Sisson, report no decrease, while Wodon, and Feinberg and Lash report normal values.

Hetenyi and Liebmann state that from 60 to 70 per cent of the calcium in the blood is in the form of ionized calcium; the rest is bound up with the albumin of the plasma or consists of non-ionized calcium salts. In 14 cases of pregnancy they found the calcium content to be between 9 and 12.6 whereas in the non-pregnant women it was between 10.5 and 12. During the last months of pregnancy there is a slight diminution in the blood calcium. All their findings demonstrate that in pregnancy there is an increased use of calcium, because of the requirements of the growing foetus and perhaps also because of a special property of the cells of the pregnant woman. Von Bodo and Liebmann examined the blood serum in eclampsia for ionized calcium, and concluded that while a decrease in free calcium ions of the blood might be responsible for the convulsions, such could not be demonstrated. They undertook this work because Lamers, Rissmann, and Kehrer had found a low blood calcium content in eclampsia and had explained the disease on the basis of a hypocalcemia. Bokelmann and Bock conclude that there is a slight decrease in calcium during pregnancy, and that during the puerperium it slowly comes back to a normal value; while the diffusible calcium in the serum is slightly increased at the end of pregnancy. Their figures are as follows: total calcium in normal non-pregnant, 9.62; first half of pregnancy, 9.75; second half of pregnancy 9.43 to 9.5 mgm. per 100 cc. of blood, while the dialysable calcium is 5.6 for the non-pregnant woman as contrasted with 5.53 to 5.54 mgm. for the pregnant. In three cases of eclampsia the total calcium was 8.08, 8.93 and 9.60 mgm. respectively, and the dialyzable calcium in the same patients was 5.45, 5.34 and 5.82 mgm. respectively. They conclude further that the total calcium, as well as the dialyzable calcium, is higher in the foetus than in the mother.

Odenthal thinks that the increased permeability in pregnancy may be associated with a disturbance between sodium and calcium ions. He found that the calcium coalescing effect during pregnancy is very slight, and held that it may be a factor in the production of capillary endothelium widening during pregnancy. Change in the pH and the relative shifting between K and Ca may be further factors in producing this change during pregnancy. From figures of all these observers one cannot conclude that a decrease in total blood calcium or in dialyzable calcium is associated with eclampsia.

Ivanyi, Rodecurt and Linzenmeier found that in eclampsia the Ca/P ratio is definitely decreased; Ca/P = 3.51 in non-pregnant; 3.46 in early pregnancy; and 2.53 in late pregnancy; while in eclampsia it was 1.87. This decrease of Ca/P in eclampsia according to their figures is due to an increase in phosphorus. Stander, Duncan and Sisson also noted a decrease in the ratio Ca/P or, as they expressed it, an increase in P/Ca, which is due to a high inorganic phosphorus value in eclamptic blood.

The other inorganic constituents of the blood, magnesium, sodium and potassium, are essentially within normal limits in eclampsia; while phosphorus is slightly elevated according to Rodecurt and Stander. The analyses of Denis and King also seem to indicate that there is no appreciable change in these elements, while the phosphorus and sulphur content of the blood are essentially identical in toxemic and normal pregnancies. One may, therefore, conclude that no marked disturbance in the inorganic elements of the blood takes place in eclampsia, except perhaps in so far as the ratio P/Ca is somewhat upset due to elevated phosphorus values.

r. Lipoids. Tyler and Underhill corroborated the work of Slemons and Stander, who showed that there is a definite increase in the total lipoids in the blood stream during normal pregnancy. Hellmuth also noted a hyperlipoidemia. Neither Hellmuth nor Slemons and Stander could find any difference in the lipoids in the toxemias of pregnancy or in eclampsia. They noted the same increase in total fats, in normal pregnant women as in those suffering from eclampsia. Ito and Kitamure found the cholesterol content of the blood to be decreased in diseases of the liver as well as in cases of nephritis. Adler and Lemmel also showed that the cholesterol content of the blood

changes in diseases of the liver, and regard the decrease of cholesterol and cholesterol-ester as indicating a disturbance of liver cells.

We may accordingly conclude that no characteristic change in the blood fats or blood lipoids is associated with the development of eclampsia. Whether the increase in fat, lecithin and cholesterol as the pregnant woman approaches term, may play a rôle in the production of ketosis will be discussed later. Up to date all attempts to connect the cause of eclampsia with a disturbance of blood lipoids have met with failure, unless the recent work on colloids should lead to more fruitful results.

s. Colloids. Colloidal chemistry has played a certain rôle in obstetrics during the past ten years. Since 1861, when Graham defined colloids as "substances which are not diffusible through animal membranes," there has been a steady development in the science of colloidal chemistry. Our old ideas of colloids have been completely changed by the work of Hardy, Jacques Loeb and others.

By the term hydrogel we denote such colloids as will solidify into a gelatinous mass with an abundance of water; and by hydrosol such colloids as are soluble in water. Colloids can usually be grouped into two classes (1) emulsion colloids, emulsoids or hydrophile colloids; and (2) suspension colloids. Proteins, starch and glycogen belong to the hydrophile class, whereas cholesterol is an excellent example of the suspension type of colloid. In an aqueous solution there is a relationship between the dissolved substance and the solvent in the hydrophile class, whereas in suspension colloids it is absent. The relationship in the hydrophile class is shown by measurement of the viscosity, which in the suspension colloids is not much altered. There is a further distinction between these two types of colloids—namely the rate of precipitation by electrolytes. Ready precipitation takes place by electrolytes in suspension colloids, whereas it is extremely difficult in hydrophile colloids. Colloids have also been classified according to their size; and particles of from 200 $\mu\mu$ (about the limit of microscopic vision) down to 1 $\mu\mu$, or 1 one thousandth μ, are said to be in colloidal state. This method of classifying colloids is, however, not very satisfactory.

The terms lyophile and lyophobe are also applied to colloids. A lyophile colloid has a tendency to unite with the dispersion medium, whereas a lyophobe has little or no tendency to become hydrated. By

the dispersion medium we mean the solution in which the colloids are present and by disperse phase we mean the particles of colloids in the solution.

Some colloids are called protective colloids and by this we mean that certain hydrophile colloids, which are precipitated with difficulty by electrolytes, have the power of protecting suspension colloids against the precipitating action of electrolytes.

A great deal of work has recently been done on the colloids of the blood during pregnancy and in the toxemias of pregnancy, and Eufinger particularly has shown that there is a definite alteration in the protein fractions of the serum during pregnancy. The ratio $\frac{\text{albumin}}{\text{globulin}}$ decreases from 2.6 in normal non-pregnant women to 0.81 in women at term; whereas the euglobulin and fibrinogen both increase as term is approached. He found by the Gerloczy reaction that there is a decrease in stability and an increase in lability of the plasma during pregnancy. Other colloids are precipitated by the very stable plasma of the newborn, whereas they are not precipitated by the plasma of the mother. Von Oettingen explains this on the basis that the very labile colloids of the mother act as protective colloids. Eufinger concludes from the work of Erich Meyer, Handovsky, Westphal and others, that the hydrophobe cholesterol fraction is of great importance as a tonic substance for the cell-membranes. We see an increase in the total cholesterol during pregnancy, but a percentage and progressive decrease of the important hydrophobe fraction up to the time of labor, a condition which, together with the protein phase-change towards the coarse dispersion side, is of great importance in the permeability and water metabolism of the cells. From the work of Overton we know that cholesterol, as a membrane-building substance, plays a part together with other lipoids on the cell-surface. There is an antagonism between lecithin and cholesterol, as the former loosens the cell-surfaces of the smooth muscle of the vessels, and the latter produces a thickening or hardening effect, which hinders the necessary lengthening of the muscle fiber after each contraction, with the result that the lowered permeability decreases the admission of water and of the swelling producing ions. When, in spite of the hypercholesterolemia in normal pregnancy, we do not have the

hypertonus, it is because of the firmer anchoring of the cholesterol in the plasma; in other words its quantitatively smaller availability furnishes an important regulatory mechanism in the pregnant organism for the maintenance of the normal tonus of the vessel. In Eufinger's opinion there results from these colloidal shiftings, which influence decisively the processes on the cell surface, the necessary lability and rapid adaptability of surface activity, which is required by the enormously varying demands of the pregnant organism. Clinically this lability in the behavior of the cell membrane is supposed to be shown in the form of the blood pressure curve in the altered response of the vessels to vasoconstrictor substances, such as adrenalin. Eufinger's work on the adrenalin blood pressure curve leads him to place in the foreground not only the state of the vegetative nervous system but also the local colloidal condition on the cell membrane as a significant influence on the form of the blood pressure.

Seitz also states that the plasma is more labile in pregnant than in non-pregnant women, although cholesterol is increased from 150 to 350 mgm. according to Chaffard, Neumann, Hermann and Hellmuth. Furthermore, there is a radical change in the composition of the cholesterol, since in non-pregnant women only 20 per cent of it is bound, while 80 per cent is readily shaken out, as compared with 40 per cent of bound cholesterol in the pregnant woman. The bound fraction is probably closely associated with euglobulin.

In eclampsia Eufinger found that $\frac{\text{albumin}}{\text{globulin}}$ ratio is still further decreased, the average value for normal pregnancy at term is 0.81, as compared with 0.21 for eclampsia. There is also a corresponding increase in fibrinogen in eclamptic patients. From these changes he assumes that there is a transfer of certain lipoids, which have been changed in their constitution, from the blood to the kidney epithelium, and that they are there eliminated. Seitz also believes that the change in the colloids of the blood is an etiological factor in the production of eclampsia.

In the toxemias there is, therefore, according to these authors, a greater disturbance in the distribution of protein fractions, the albumin being decreased and globulin and fibrinogen increased. Kaboh and Runge believe that the oedema depends on the lowering of the al-

bumin in the plasma. Seitz asserts that there are two types of eclampsia—one with very low albumin fraction in the serum (0.69 gram per cent) and the other type in which it is not so markedly reduced. In the first type the symptoms are severe and the mortality high, while the second type is mild, and is designated as "Labilitätseklampsie," by Seitz.

t. Carbohydrates. Without going into the chemical details of the methods of determining the blood sugar, it is essential, before discussing the sugar level in eclamptic blood, that it be pointed out that during the past ten years remarkable improvements in methods have been brought about by such chemists as Folin and Benedict. Stated briefly, the main desideratum in determining blood sugar is to employ a copper reagent which will not be affected by unknown non-glucose substances which have reducing powers. Formerly these bodies, as well as glucose, were included in the estimation, but gradually we have approached more closely to the true glucose value. This is rendered apparent by the fact that only a few years ago 100 mgm. of sugar per 100 cc. of blood was regarded as normal, whereas by the most recent method of Benedict this value has been reduced to about 60 mgm. It is, therefore, obvious that in comparing the results of different investigators one must know exactly what method of determination was employed before one can intelligently correlate findings.

Benthin, Walthard, Obata and Hayaski, Stander, Duncan and Sisson, Wieden, and others have reported hyperglycemia in eclampsia. Most of these authors explain the elevated blood sugar on the basis of the convulsions, since we know that muscular work raises the blood sugar. Stander and Radelet, however, found that the elevation often persists for an appreciable time after the cessation of the eclamptic convulsions, and Stander is inclined to think that added factors, such as changes in the hydrogen-ion concentration in the liver cells, may influence the production of a hyperglycemia. From figures submitted to him in personal communications from a number of clinics in this country, as well as from his own findings, which cover approximately 120 eclamptic patients, the author believes that the blood sugar values in eclampsia are sometimes within normal limits, often show a definite hyperglycemia, but never a hypoglycemia. He holds that in eclampsia there is a definite tendency towards hyperglycemia, in

contradistinction to Titus and his co-workers and Levy who report hypoglycemia. The following table shows the average, as well as the limits of, blood sugar level in eclampsia as observed in Baltimore, Pittsburgh and Los Angeles.

Blood sugar in eclampsia

AUTHOR	NUMBER OF CASES	AVERAGE	LIMITS
		mgm.	*mgm.*
Stander	94	102	44–190
Lazard	12	115	87–166
Miller and Martinez	19	105	75–181

Our findings in the above table were obtained by three different methods of determination, and where the latest Benedict method, which gives from 60 to 80 mgm. per 100 cc. blood for normal individuals, was not employed, the values were corrected to this standard. The findings from the other two clinics were submitted in personal communications, were not corrected and are based on 80 to 100 mgm. as the normal value.

Titus and his associates found that in serial blood sugar readings, during an attack of eclampsia, wide fluctuations occurred in the blood sugar within exceedingly short intervals of time. They found that the convulsive seizure occurred at levels which Titus calls relative hypoglycemia, and he holds that the fits are apparently the cause of the sudden drop in blood sugar; and that following them, there is usually a temporary rise in the blood sugar. Titus, Dodds and Willetts, in their recent contribution write:

"As a result of this and previous studies of toxemic disturbances of pregnancy, we are led to conclude that there is a relationship between all toxemias of pregnancy; that the difference between the hepatic lesions of the various clinical states is less distinctive than has generally been supposed; that there is no specific toxin; toxicoses of pregnancy, particularly eclampsia, are due to disturbances in maternal metabolism; and that the disturbance is one of carbohydrate metabolism, based primarily on a deficiency in carbohydrate intake plus increased consumption of carbohydrates which results in a depletion of the glycogen stores with consequential damage to the liver and its functions.

"This glycogen deficiency in the liver presently becomes equivalent to its partial 'extirpation;' the blood sugar values begin to seek hypoglycemic levels followed by frenzied efforts towards recovery, thus initiating the fluctuating waves noted in our charts; the convulsions which occur at certain low levels as the fluctuations become more and more violent are controllable, like the familiar hypoglycemic convulsions by glucose injections.

"The nephritis of preeclampsia and eclampsia, as well as grave hyperemesis, is not the forerunner but an incidental symptom and result of the intoxication.

"The insulin production of a nondiabetic pancreas may be temporarily in abeyance during a pregnancy intoxication as a physiologic responsibility to the lessened glycogen reserve in the body. Such a pancreas should respond to an injection of glucose as does any normal pancreas by an overproduction of endogenous insulin so that any additional insulin injected is an additional overdose."

The author has attempted to corroborate the findings of Titus, by studying the blood sugar at five minute intervals in eight eclamptic patients. The final results will be reported elsewhere, but it may be stated that he was unable to observe a relative hypoglycemia in any of them.

Scontrino determined the amount of free and combined blood sugar, and in normal pregnancy observed that there is an increase in the amount of free blood sugar during the first six months, a decrease during the last three months, and an increase during labor. In eclampsia there is an increase in the amount of free sugar, as well as of combined sugar during the attack. In this connection, it may be interesting to mention the work of John, who analyzed 22,808 blood sugar estimations in non-diabetic patients. He found 2452 that showed a blood sugar value below 80 mgm. per 100 cc., in 1791 it was 75 mgm. or below, while the lowest value was 30 mgm. per 100 cc. He holds that such a high percentage (11 per cent) of blood sugar below 80 mgm. per 100 cc. of blood, indicates that such low values are not so rare, and are apparently normal for the individuals concerned, as none of them presented any special complaint.

Bockelmann, Rother and others have assumed that it is possible for the human body to transform fat into carbohydrate, and furthermore

believe that this function takes place primarily in the liver. On the other hand, in a recent contribution Deuel and Milhorat state that there is no convincing proof that mammals are able to convert the fatty acid fraction of the fat molecule into carbohydrates. They were unable to demonstrate that acetic acid is a glucogenetic agent, nor was there any appreciable synthesis of glucose from sodium acetate when that substance was introduced subcutaneously or intraperitoneally into phlorhizinized dogs. In their control animals, the injected glucose was excreted almost quantitatively, and this would presumably indicate that, if glucose had been formed from the acetate, an extra amount of sugar would have been excreted in the urine.

Gottschalk and Nurnberger both believe that the glycosuria of pregnancy is due to a change in the permeability of the kidneys, and the former is convinced that the carbohydrate metabolism is decreased or slowed down during pregnancy. Lavake in 1916 suggested that a high carbohydrate diet might be of value in pre-eclamptic toxemia, as well as the administration of oxygen, as advocated by Stroganoff. Host writes that there is a curious and characteristic difference in the blood sugar during the first and second periods of pregnancy. Early in pregnancy, the kidney threshold for sugar is normal and the blood sugar is often remarkably high, so that when glycosuria occurs it is often associated with hyperglycemia and is not, as is generally believed, of renal origin. On the other hand, in the latter part of pregnancy, the blood sugar rise is usually very small, but the renal threshold is low so that glycosuria frequently occurs; and when it does it is probably renal in origin. This author suggests that the corpus luteum causes the sugar rise which is characteristic of early pregnancy, while the low renal threshold in the latter months appears to be dependent on the foetus or the placenta. Benthin, Walthard, Frey, Herold, Hellmuth and Guggisberg have all found low blood sugar values during the second half of pregnancy.

In labor there is usually an increase in blood sugar as was clearly demonstrated by Schmidt, Bickenbach and Jonen. These investigators studied the glycogen content of the liver and the muscles of dogs during pregnancy, and found in the normally fed animal a decrease in the relative weight of the liver at the end of pregnancy. The amount of glycogen in the liver of a normal well fed dog, getting

75 calories per kilogram of body weight, is approximately 6 per cent, whereas at the end of pregnancy it falls below 2.15 per cent. They also noticed that the fattest dog showed the greatest decrease in the glycogen content of the liver, which averaged 57 per cent of the normal value. They likewise found a similar decrease in the glycogen of the muscle throughout the body. They further analyzed for fat and observed that the fat content in the liver is sometimes but not always increased during pregnancy. They refer to the work of Delle Chiaie, who obtained similar results. In general, it may be said that when an increase of fat occurs during pregnancy it is not to be regarded as a degenerative process, but rather signifies a liberation of fat from the fat depots without injury to the cells. That there is a functional disturbance of the liver during pregnancy has not been definitely shown although these authorities believe that there is a change in the function of the "chemical organization" of the cells of the liver.

An increase in fat in the blood stream during pregnancy has been demonstrated by Capaldi, Herman and Neumann, Decio, and Slemons and Stander. Schmidt, Bickenback and Jonen regard this change as convincing proof that fat is liberated from the fat depots and is ready for utilization in the liver. Bockelmann and his co-workers have demonstrated that there is an increase in acetone bodies in the toxemias of pregnancy. Acetone bodies can be produced in only two ways, —either out of protein metabolism from amino acids, or from fat metabolism. The changes just mentioned, the glycogen decrease in the liver and muscles, the fat increase in the blood stream and liver, and the increase in acetone bodies—are regarded by Schmidt, Bickenback and Jonen as proof that carbohydrates are built in the liver from fat. As a sign of the liberation of fat for this purpose, we have the lipaemia, already referred to; and as a sign of the transfer of fat into carbohydrates, we have the acetone bodies. If the fat content of the liver becomes too great, which can be produced by a severe glycogen decrease and which is particularly common in very fat animals, then a disturbed liver function may develop.

The liberation of fat from the fat depots, as well as the splitting of fat, can go on undisturbed in the face of a severe glycogen shortage, but this is not true as far as the building up of new carbohydrates from fat is concerned, and when this occurs it is associated with the

production of acetone bodies. These authors state that the glycogen decrease must reach a certain degree before the process of manufacture of carbohydrates from fats is started.

To explain glycogen deficiency in both liver and muscle at the end of pregnancy, these authors invoke the influence of the vegetative nervous system. For example, Herold believes that vagotonia is responsible for the hypoglycemia at the end of pregnancy. Schmidt, Bickenback and Jonen, however, do not believe that it is responsible for the glycogen decrease noted in the liver and muscles, but hold that it can only be explained on the basis of an over-action of the sympathetic nervous system. Moreover, they believe that stimulation of the parasympathetics results in glycogen building in the liver, and as there already exists an increased stimulation of that system during pregnancy, it is impossible to explain the decreased glycogen in the liver at the end of pregnancy as the result of vegetative nervous disturbances. Consequently, we must seek another explanation, and these authorities hold that the decrease in glycogen can only be explained by a waste or burning up of the glycogen in the mother. The consumption of glycogen at the end of pregnancy must be more intense than in the non-pregnant woman. We do know that the respiratory quotient is increased (Magnus-Levy and Zuntz). Mahnert has shown that protein is spared during pregnancy and believes that with the burning of fat the carbohydrates are used in greater amounts. It is not so easy to prove that carbohydrates are wasted during pregnancy. The weight of the liver is of some importance, and that organ must do more work per unit of body weight than in the non-pregnant person. These authorities also examined the liver histologically and could find no changes at the end of pregnancy. There was undoubtedly fat infiltration in the liver cells, and particularly in their center, and such cells showed no glycogen. It would, therefore, appear from this work, that in normal pregnancy the liver shows signs of glycogen depletion, but that such a carbohydrate lack is the basis for the development of eclampsia has not been proven.

u. Acidosis. We know that in normal pregnancy there is a decrease in the CO_2 combining power, to approximately 44 volumes per cent, so that it is customary to speak of the "acidosis of pregnancy." Bock determined the hydrogen ion concentration for normal pregnancy and

found it to be 7.51 in the early months as compared to 7.52 for non-pregnant women. In the last months of pregnancy the pH of the blood dropped to 7.47, but during labor and the puerperium the average was 7.52. He concludes that during the last weeks of pregnancy there is an actual change in the reaction of the blood, and that this is brought about by the buffer capacity of the blood. He also believes that the amphoteric buffer substances, such as protein bodies, play an important part in this change. Schmidt and Wingen analyzed the gases of the blood and attempted to show that the large carbohydrate requirement during the latter part of pregnancy is partly met by the conversion of fat into glycogen, and that during this transformation acid by-products are liable to appear. These acid by-products require a certain amount of the alkali reserve of the blood for neutralization, and so lower the blood's capacity to bind CO_2 with a resulting lower alveolar CO_2 tension.

Gaebler and Rosen made a careful study of the acid base balance during pregnancy. They determined the alveolar CO_2 combining power, plasma bicarbonate, and the plasma pH, and found that during pregnancy the reaction of the plasma is slightly more alkaline than normal, though the plasma bicarbonate is lower than in the non-pregnant. Early in the puerperium the bicarbonate value increases, while the reaction of the plasma becomes more acid. The plasma pH values observed by them during pregnancy are not as alkaline as those found by Marrack and Boone, but the quantitative results are very similar. Vozza states that in the pregnancy toxemias, acidosis is the most conspicious finding, and that it is very pronounced in many eclamptic patients. He bases his conclusions on 200 determinations of the alkali reserve of the blood in various periods of normal and abnormal pregnancy.

MacNider found that in normal pregnant animals there is a definite tendency of the acid base equilibrium of the blood to become disturbed and that such a disturbance is more marked and more frequent in old than in young animals. He feels that this change is not dependent on renal injury and therefore is not a retention phenomenon. He concludes from a large series of experiments that, associated with gestation, there is a definite tendency towards failure to maintain a normal cida base equilibrium.

In eclampsia, the CO_2 combining power is still further decreased and it is not unusual to see values below 30 volumes per cent. The author believes that probably the lowest values for the CO_2 combining power ever observed sometimes occur in eclampsia, and he has noted it as low as 12 volumes per cent. Hasselbalch and Gammeltoft examined the blood of four eclamptic women and found in two cases that the fixed acidity of the blood was increased with an uncompensated acidosis, while in the other two cases the hydrogen ion concentration of the blood was normal. Bokelmann and Rother also found the CO_2 combining power in the blood lower in eclampsia than in normal pregnancy, and agree with Stander that the severity of the condition often seems to depend upon the degree of acidosis.

In eclampsia there is an increased production of acid bodies. Zweifel and Scheller found an increase in lactic acid in the blood and cerebrospinal fluid of three eclamptic women three to eight hours after a convulsion. These authorities are of the opinion that the increase in lactic acid in the spinal fluid may play a part in the production of the acidosis of pregnancy. Zweifel, Bockelmann, Kienlin, Loeser, Schultze, and Stander and Radelet have all reported increase in lactic acid in eclampsia. Some believe that this increase is associated with liver damage. In this connection it is interesting to note that Noah found that only in extensive destruction is the carbohydrate assimilating function of the liver disturbed to such an extent that there is an abnormal accumulation of lactic acid in the blood stream. Perger states that the increase in lactic acid is often due to a disturbance of the resynthesis of that acid by the muscles. The high lactic acid in eclampsia, may, therefore, be due to muscular work, damage to the liver cells, or to a disturbance in the resynthesis of glycogen from lactic acid following incomplete oxidative processes.

Amino acids have been proposed as a cause of eclampsia. Ewing and Wolf, because leucine and tyrosine had been found in the urine of eclamptic women, and because they themselves had found a decrease in urea and an increase in the undetermined nitrogen in the urine, suggested that amino acids were incompletely metabolized in the liver and were the cause of the toxemia. Murlin and Bailey found on the contrary, that not only the amino acid fractions but also the other

nitrogen fractions of the urine were usually within normal limits in eclampsia, and concluded that the nitrogen distribution in the urine was not of great help in the diagnosis of the disease. Furthermore, Losee and Van Slyke have analyzed the total amino acid nitrogen in eclampsia, and conclude that the toxemias of pregnancy can be attributed neither to failure in deaminization of the amino acids, nor to the moderate degree of acidosis observed in these cases.

In eclampsia, B-oxy-butyric acid may exert a toxic effect, not only because of its acid property, but also as a specific poison on the metabolism, as shown by the work of Harpuder and Erlsen.

In eclampsia, then, we have an acidosis, and usually a hyperglycemia. It is interesting to note that Bokelmann and Rother have shown that in two cases of eclampsia which came to autopsy, no glycogen could be demonstrated microscopically in the liver. Brinker has shown that it is possible to produce hyperglycemia in rabbits, by increasing the hydrogen-ions. He has also shown that the liver is not the only organ that plays a rôle in this mechanism; the liver, muscles, and also the kidneys will give up a great amount of sugar when placed in an acid medium, while an alkali medium will have the opposite effect.

Hamburger and Brinkmann demonstrated that the permeability of the kidneys depends upon the pH of the blood. From this consideration Bokelmann concludes that the hyperglycemia probably depends upon a disturbance in the acid base equilibrium. There are, of course, others who think that the changes in carbohydrate metabolism in pregnancy are due to the action of adrenalin; but from the work of Underhill, Cleissel and others, it seems that in human beings the adrenalin glycosuria depends upon the reaction of the blood, and that the glycogen mobilization action of adrenalin is weakened by alkalies and augmented by acids. Elias-Sammartino showed that by injecting adrenalin in rabbits, there developed a glycosuria as well as a decrease in the acid combining power of the blood; and that adrenalin will produce an increased amount of lactic acid in the liver. If, therefore, we accept the theory that there is a general hypertrophy of the endocrine glands, with a resulting increase in adrenalin secretion it becomes possible to explain the acidosis of pregnancy in an indirect way, namely

that the adrenalin causes an increased production of lactic acid with a subsequent increase in acidosis.

The acidosis undoubtedly has an effect on the blood vessels. Bokelmann states that when acid is introduced into the stomach of the rabbit, the alkali of the organism is decreased, and an increase in vaso-constrictor substances in the blood follows. Also, Kretschmer was able to increase the action of adrenalin by an intravenous injection of acid. Balin and Goldsmith have also shown that in acidosis the effect of adrenalin on vessels is increased, which is the reverse of what takes place in alkalosis, as shown by Druz and Fritz. But it is possible that the different acids may have a different effect. An increased CO_2 content of the blood never has a vaso-dilator action, while organic and inorganic acids have a vaso-constrictor action. On the other hand, we learn from the placenta perfusion experiments of Fleisch, Atzlar, Lehmann, and Schmidt, that the hydrogen-ion concentration has a vaso-dilator effect. As small a change in pH as 0.21 will alter the caliber of the vessel wall, according to these authors. The nervous system also reacts to a minimum change in pH, as shown by Bethe.

In eclampsia, if there is a great disturbance in the pH in the blood, as indicated by the work of Gammeltoft and Hasselbalch, the acidosis must act on the breathing center, as well as on other centers. The motor disturbances resulting in convulsions and coma, may be directly the result of this changed pH according to Kautsky. Bokelmann states that the changes in hydrogen ion concentration will produce hypertension, and if the peripheral vascular system is unable to take care of the blood flow, there will follow a decrease in the elimination of acid valencies; in such circumstances the amount of blood supplied to the brain increases and leads to congestion of the cerebral capillaries.

There is an antagonism between the various ions, but whether this plays a part in the acidosis of pregnancy or of eclampsia is not clear. We do know that an alkalosis leads to a decrease in calcium ionization, and it is possible that in the acidosis of pregnancy the ionized calcium increases at the cost of the bound calcium. In this connection the work of Rodecurt and Reginsburger is of interest. They found that the ultra-filtrable calcium and potassium decreased in eclampsia, while

there was an increase in sodium and in the $\frac{K}{Ca}$ ratio. The non-diffusible calcium is that type of calcium which is bound to protein, according to Rona. From the experiments of Kraus and others, it seems that the condition of the vegetative cells depends upon the equilibrium of anions and cations. Potassium has a para-sympathetic or vagal action, while calcium has a sympathetic action. Driesel states that the effect of acid bodies is to cause more calcium ions to be thrown out of the blood into the tissues. The decrease of the calcium in the blood, which is seen in sympatheticotonic conditions is explained on the basis that, as a result of the local acidosis, there is an increased amount of ions in the blood and this leaves the blood to go to the tissues. There further appears, according to Bokelmann, to be some connection or association between primary acidosis and decrease of blood calcium and the condition known as "sympatheticotonia." He states that there also appears to be a connection between the high blood pressure following increased adrenalin production and the tetanic contractions or convulsions; and it is even possible that there is a connection between the amount of hormone substances produced and the calcium, potassium and hydrogen-ions, as suggested by Zondek. There may also be a connection between carbohydrate metabolism and in particular lactacidogen, and the cations, as proposed by Emdem; calcium salts bringing about a synthesis and magnesium salts having an opposite effect.

Rossenbeck examined four cases of eclampsia for the chloride, sodium, calcium and potassium content of the blood and noted that the equilibrium between the sodium and chloride ions is definitely altered. He believes that the acidosis in eclampsia is caused not only by an over production of acid metabolites, but also by a definite decrease in alkali. This alkali deficit or alkalipenia further disturbs the processes of oxidation. The cause of this shifting in the ions is attributed by this author to a hyperfunction of the hypophysis, which causes sodium to leave the tissues. As a result of muscular contractions or convulsions, phosphoric and lactic acids are set free and these two acids could be drawn into the tissues in order to neutralize the accumulated sodium and so make it possible for the sodium to be

transformed back into the circulating blood stream. The acidosis of the blood stream could be combated by the increased washing out of the phosphoric acid in the form of secondary phosphates, according to Rossenbeck.

Beck states that in the pre-eclamptic state, the pH of the blood is the same as in normal pregnancy, while immediately before convulsions the pH is altered. During the attacks the pH may change as much as to 7.28 (pH normal blood 7.44), returning to normal during the puerperium. Beck believes that the change in pH is not associated with the cause of the convulsions, but is the result of muscular activity.

Although the complete acid-base equilibria formula has not been worked out for eclampsia, the data up to date seem to indicate that there is a marked disturbance in the oxidative processes, and that this is associated with an acidosis which may often become "uncompensated." We are as yet unable to state that this disturbance is the cause or the effect of the eclamptic outbreak, but it undoubtedly offers us one of the most promising fields for further work concerning the etiology of the disease.

v. Hypertension. As the increased blood pressure is one of the most outstanding characteristics in the majority of cases of eclampsia, many attempts have been made to explain its production on the basis of a toxin circulating in the blood stream. Volhard, Hülse, Becker, Hussey and others have worked on this theory. Volhard and Hülse have attempted to demonstrate that there are substances in the blood stream which make the vessel walls more sensitive to constrictor bodies in cases of hypertension. Hussey, on the other hand, believes that there are substances in the blood stream in hypertension and eclampsia which act directly as vaso-constrictor bodies on the vessel walls. These authors have speculated as to the nature of these different substances, and Volhard is of the opinion that they may be amines. In this connection it may be interesting to note that Hofbauer has suggested that histamine may play an etiological rôle in eclampsia. Tyramine has also been suggested by Johnston and Johnson as a causative factor in the toxemias of pregnancy. They base their contention on the fact that in a case of eclampsia, the vomitus, blood and placenta all showed the presence of tyramine. Stander, in attempting

to corroborate the findings of Hofbauer, was unable to produce the typical liver lesions of eclampsia in animals by the administration of histamine, and summed up his findings by saying "Peptone, albumose and histamine produce a blood picture suggesting anhydremia, and the evidence so far adduced both clinical and pathologically makes it improbable that any one of them is to be regarded as an etiological factor in the causation of eclampsia."

The search for, and isolation of, a toxin in the circulating blood, which will explain the etiology of eclampsia has so far been unsuccessful, and this field still remains an interesting and important one for further investigation.

Krogh in his studies on capillaries has found that colloids are not diffusible through the capillary endothelium, but that the capillaries may become permeable to them under certain conditions. Normally the capillary wall is impermeable to albumin and this is of great importance in the movement of fluid to and from the blood stream. Grzechowiak has measured the capillary pressure by means of the Kylin apparatus and found that while during normal pregnancy the capillary pressure is at first low and during the latter months approximately normal, it increases quite markedly in eclampsia.

It was formerly supposed that fluid passed from the blood vessels to the tissues by simple filtration. Recent work, however, indicated that factors other than simple filtration influence the passage of fluid. We now know that the rate of filtration through the capillary wall is directly proportional to the excess of capillary pressure over the osmotic pressure of the plasma proteins. These two forces—capillary pressure and osmotic pressure—work in opposite directions. Landis has stated that the increased permeability of the capillary wall may be accounted for by lowered oxygen tension, increased carbon dioxide tension or by local increase of permeability to the passage of protein through it. The lack of oxygen, in addition to indirectly affecting the tissue metabolites, also increases the permeability of the capillary wall and so permits the rapid filtration of fluid and the passage of plasma protein.

Yunoki and Uchino injected Congo red into gravid and non-gravid rabbits, as well as into pregnant and non-pregnant women and women

suffering from the late toxemias of pregnancy. In pregnancy they noted a delay in the speed with which the Congo red was absorbed from the serum both in rabbits and women, and the absorption was greatly retarded in women suffering from toxemia of pregnancy. Obata and Benda have recently advanced the theory that eclampsia is caused by a functional insufficiency of the reticulo-endothelial system. From the work of Ribbett and Goldmann we know that the reticulo-endothelial cells readily absorb colloidal acid-pigment granules. It would therefore seem that from the results of Yunoki and Uchino there is an insufficient function in eclampsia of the reticulo-endothelial system.

w. Summary. Eclampsia is very seldom associated with nitrogenous retention in the blood, and where the non-protein nitrogen is elevated it is probably the result of kidney injury caused by the eclamptic outbreak. The same holds true for the blood urea nitrogen. An increased uric acid and decreased CO_2 combining power are the outstanding findings in the blood chemistry in eclampsia. The blood sugar is sometimes normal, but is often elevated according to most authors; although some claim that hypoglycemia invariably accompanies the disease. The author believes that the weight of evidence is in favor of a normal or elevated blood sugar. Blood lactic acid is elevated in eclampsia. There is some controversy regarding amino-acids in the blood, but it appears that the disease is not associated with disturbed deaminization. The polypeptide nitrogen has not been satisfactorily worked out. Creatin and creatinine metabolism is not markedly upset. The blood chlorides show a disturbance where the disease is accompaneid by oedema. The only abnormal finding in the cations is a slight elevation in the $\frac{P}{Ca}$ ratio, due mainly to an increased phosphorus. The blood colloids reveal a disturbance consisting of a shifting in the protein fractions in favor of globulin, fibrinogen and euglobulin at the expense of albumin. Fats and lipoids show no greater disturbance than is noted in normal pregnancy. The very meager work on the hydrogen-ion concentration of the blood in eclampsia points to a true acidosis in some cases. No toxin in the blood or urine has been isolated. The only abnormal finding in the urine is a

slight upset in the nitrogen partition due to a decrease in the urea nitrogen. The various blood disturbances so far noted seem to be inter-related, and deficient oxidative processes probably play a major rôle.

Symptoms of eclampsia. The eclamptic entity is well known and a description of the symptoms, convulsions and semi-comatose or comatose condition seems unnecessary. It should be pointed out, however, that there are certain prodromal symptoms which serve as danger signals to those able to interpret their significance. Even in the absence of an increase in blood pressure or of albumin in the urine, the occurrence of very sharp epigastric pain, partial or complete amaurosis, or other visual disturbances, severe occipital headache and dizziness should make one suspicous of the pre-eclamptic condition; and all gravid women should be instructed to report immediately to their physician, should one or more of these symptoms make their appearance. It has been found that the diastolic blood pressure is often an earlier index of an impending eclampsia than is the systolic blood pressure. The earliest upset in the chemical constituents of the blood will usually be found in the uric acid and CO_2 combining power. The normal uric acid value ranges between 2 and 3.6 mgm. per 100 cc. of blood. Invariably one sees uric acid values of 5 to 8 or 9 mgm. in cases of eclampsia. Early in eclampsia or even in the pre-eclamptic state, uric acid may be as high as 5 or 6 mgm. per 100 cc. of blood. A patient presenting one or more of the above symptoms and showing an elevated uric acid content of the blood, with a CO_2 combining power below 35 volumes per cent, should be treated with caution and regarded as a potential eclamptic.

The eye findings in eclampsia present a very interesting field for speculation. It has been known for a long time that eclampsia is often associated with visual disturbances such as spots before the eyes, partial or even complete amaurosis. Santonsatso writes that in eclampsia the blindness may be associated with ophthalmological changes, as well as with a decrease in the intra-ocular pressure, but that in some cases no opthalmological changes can be noted. Cheney made fundus examinations in a large series of cases of toxemias at the Boston Lying-In Hospital, and feels that such routine examinations

are of distinct value. The most common eyeground findings are detachment or oedema of the retina, choked disc and inflammation of the choroid, acording to Hirsch. These conditions have a more favorable prognosis in the pregnant than in the non-pregnant woman. Hirsch also states that in eclampsia serious visual disturbances may develop, and yet the eye grounds may appear normal, and he thinks that the amaurosis in such cases is due to a disturbance in the visual centers of the brain. He found in 538 cases of eclampsia, 15 with total blindness and 13 with high grade amblyopia. Traymann reports a case of post-partum eclampsia with asymmetric hypertrophy of the hypophysis and thinks that the asymmetry of the sella turcica or perhaps hyperemia of one half of the hypophysis may be the cause of the hemianopsia observed. He advocates paying more attention to the eyes during pregnancy, as amaurosis may be the first sign of an impending toxemia.

It should be noted that eclampsia has also been described in cases of tubal pregnancy. Ebeler reported the case of a primipara 23 years old, from whom a right ruptured tubal pregnancy was removed. Within 10 hours after the operation she developed convulsions and the urine showed a large amount of albumin as well as casts. The patient died the next day with the diagnosis of eclampsia. He also refers to three other cases of extrauterine pregnancy associated with eclampsia.

Treatment of eclampsia. From about 1840 to 1870 the treatment of eclampsia consisted mainly in venesection, sedatives, cold packs or baths, but no obstetrical interference. Eden writes that from 1870 to 1890 the treatment was still expectant and that narcosis, diaphoresis and pilocarpin played a great part, but venesection was abandoned because Schroeder had pointed out that the blood pressure fell only temporarily after it. At about this time the current teaching was to the effect that the best results were obtained after the promptest possible delivery, which was effected by means of accouchment forcé and instrumental dilatation of the cervix. The maternal mortality for this period was over 30% where statistics were available. When the hepatic theory as to the causation of eclampsia came into vogue, Dührssen in 1890 advocated Caesarean section as the routine treatment for all cases of eclampsia, urging that the operation be performed as soon as possible

after the first convulsion. Shortly afterwards vaginal Caesarean section was introduced by him, and from that time on the radical treatment of eclampsia has been followed by many. At about the beginning of the present century a tendency developed toward the employment of more conservative methods of treating eclampsia because of the very high mortality following the use of vaginal and abdominal Caesarean section. These endeavors started in Europe and gradually came into use in England and the United States. Today there is still a great deal of controversy as to the relative merits of the two methods of treatment—the operative or radical and the medical, or conservative.

a. Pre-natal care. It has generally been recognized that pre-natal care is an important factor in preventing the occurrence of eclampsia, as well as in reducing the maternal mortality from it. In an excellent statistical study comprising over 42,000 deliveries, Rice showed that in patients who had received pre-natal care the incidence of eclampsia was only one in 1652 cases, as compared with a general incidence of about one in 200 deliveries in lying-in hospitals, as indicated above. The treatment of eclampsia may be divided into two types—the prophylactic and the curative. It is evident that a great deal can be done by careful pre-natal study of all pregnant women wherever this is possible. The frequent routine examination of the blood pressure, of the urine and of the patient's general condition, undoubtedly leads to the early recognition of a pre-eclamptic state or an eclampsia that may be pending. From our experience in this clinic we are convinced however, that prophylaxis alone cannot entirely prevent the outbreak of eclampsia, though it may be a great aid in reducing the incidence and the maternal mortality of the disease. Kaner, Williams and others are firm believers in the value of prophylaxis.

Nonaka, also an advocate of prophylaxis in eclampsia, suggests a diuretic-cardiotonic method of treatment in which he gives sodium theocine mixed with digalen and dissolved in a large amount of water; and his patients are made to drink this solution very slowly. He reports excellent maternal results.

b. Radical treatment. Until recently radical treatment was the general method of treatment and today there are three main schools,

each claiming that its method of treatment gives the best results. These are (1) Radical treatment; (2) Conservative treatment; and (3) A combination of radical and conservative. There are also various special treatments which will be taken up in detail.

Reuben Peterson is a very strong adherent of the radical treatment of eclampsia and recommends abdominal Caesarean section in treating ante-partum eclampsia. In 1914 he reported 530 cases of eclampsia treated by Caesarean section with a maternal mortality of 23.4 per cent. Waldstein reports 117 cases with a maternal mortality of 1.7 per cent. In 29 per cent of these cases he performed Caesarean section. Manna believes that in severe eclampsia, the best treatment is Caesarean section together with internal medication. Llames-Massini, who reports 92 cases of eclampsia, in 14 of which he performed Caesarean section with no maternal deaths, is a strong advocate of radical treatment.

Fuerst states that the best method of delivery in eclampsia is by transperitoneal cervical Caesarean section. In 238 cases he had only 9 maternal deaths, and as he believes that few of them could not be attributed to the method, he calculates his maternal mortality at 2.1 per cent. He does not place as much emphasis on the time consumed in performing the operation as does Wagner, who urges great speed in operating and states that no operation should take over twenty minutes. Stoeckel is a staunch believer in the Caesarean section treatment of eclampsia, and he reports a maternal mortality of 8.4 per cent in a series of 119 cases so treated.

Brodhead does not believe that abdominal section is always justifiable in the treatment of eclampsia. When one has to deal with a dead or non-viable child and the patient is in labor with a cervix partly dilated and is not in a hospital, Caesarean section is definitely contraindicated. He believes, however, that with more experience in a considerable number of cases Caesarean section may be the safest and most satisfactory way of treating eclampsia.

c. Conservative treatment. Plass in a very excellent review of the subject has compiled the following table to represent the results obtained in over 10,000 cases by these two methods, radical and conservative.

The Maternal Mortality of Eclampsia under the Active as Opposed to the Conservative Method of Treatment

AUTHOR	YEAR	NUMBER OF CASES	DEATHS	
			Number	Per cent
Active intervention				
Peterson	1911	530	124	23.4
Fruend	1912	551	95	17.2
Zweifel, P	1913	623	111	17.8
Peterson	1914	283	73	25.8
Brown	1916	6	1	16.7
Cragin	1917	251	71	28.3
Ruge II	1917	354	67	19.0
Brodhead	1918	302	53	17.5
Parke	1918	21	2	9.5
Poucher	1918	4	1	25.0
Brandt	1918	156	26	16.7
Kerr	1921	236	71	30.1
Stevens	1922	9	3	33.3
Eden	1922	93	25	26.9
Hirst	1922	17	3	17.6
Kellogg	1922	103	27	26.2
Zweifel, E	1923	204	38	18.6
Englemann	1923	59	18	30.3
Beck	1924	26	7	26.9
Langrock	1924	34	12	35.3
Lawrence	1925	5	3	60.0
King	1925	62	20	32.3
Wilson	1925	110	25	22.7
Davis and Harrar	1926	495	115	23.2
Greenhill	1926	78	6	7.7
		4,607	997	21.7
Conservative therapy				
Knipe and Donnelly	1916	59	10	17.0
Brown	1916	15	1	6.7
Cragin	1917	138	20	14.5
Ruge II	1917	213	31	14.5
Fruend	1917	168	24	14.3
Moran	1922	29	2	6.9
Stevens	1922	14	1	7.1
Solmons	1922	204	21	10.3
Hirst	1922	72	13	18.1
Zweifel, E	1923	107	8	7.5
Englemann	1923	244	27	11.1

AUTHOR	YEAR	NUMBER OF CASES	DEATHS	
			Number	Per cent
Conservative therapy—Continued				
Zweifel, P.	1923	317	27	8.5
Hingston and Mudaliar	1923	459	81	17.6
Beck	1924	38	7	18.4
Bunzel	1924	54	6	11.1
Langrock	1924	66	16	24.3
Hinselmann (Stroganoff)	1924	3,302	307	10.8
Lawrence	1925	28	7	25.0
King	1925	7	0	00.0
Wilson	1925	137	14	12.8
Alton and Lincoln	1925	4	1	25.0
Speidel	1925	11	2	18.2
Davis and Harrar	1926	149	23	15.4
Dorsett	1926	38	2	5.3
Lazard, Irwin and Vruwink	1926	103	14	13.6
		5,976	665	11.1

His tabulation shows that in the 4607 cases treated radically the mortality was 21.7 per cent, as contrasted with 11.1 per cent in 5976 cases treated conservatively. In other words, the mortality was reduced by nearly one half in the conservative series.

Plass writes

"At present there can be no question but that the regular treatment for eclampsia should be conservative, with radical surgical procedures reserved for the unusual cases with complications which themselves afford indications for operative delivery. One fact which should recommend this conclusion to you all is that conservative treatment may be carried out in the home with little added risk, whereas under such circumstances the danger from operative intervention is markedly increased. Ideally, all eclamptics should be treated in hospitals, but that is not yet possible, and it should be very consoling to the rural practitioner to know that he can, when necessary treat his eclamptic patient in the home by medical means and yet be following the best medical teaching.

There seems very little to choose between the various conservative treatments in vogue. They all give practically the same results in the hands of their exponents. Tweedy and the Dublin School have relied upon elimination and starvation. Stroganoff upon morphine and chloral, and Lichenstein upon copious venesection. The routines advocated by American

authors are mostly based around these three methods, but usually with rather essential modifications, dictated by some peculiar slant of the individual. The Stroganoff procedure is the simplest and therefore the most widely applicable, since it may be carried out away from a hospital and independent of any elaborate equipment."

It is impossible to review in detail the work of the various advocates of these two methods. In a discussion on the use of magnesium sulphate Stander compiled the following table indicating the end results obtained in 12 obstetrical clinics with radical and conservative treatment, respectively. From it one will see that although the conservative method of treatment usually gives better results as far as the maternal mortality is concerned, the fact cannot be ignored that certain clinics are obtaining excellent results with radical methods of treatment.

Gross maternal mortality in eclampsia

AUTHOR AND CLINIC	NUMBER OF CASES	TREATMENT	MORTALITY
Stoeckel—Leipsig	119	Radical	8.4
Leidenius—Helsingfors	250	Radical	14.2
Davis and Harrar—New York Lying-In	370	Radical	20.0
	149	Conservative (venesection)	15.0
Miller and King—New Orleans Charity Hospital	138	Radical	47.8
	38	Conservative (mod. Stroganoff)	15.8
Williams—Johns Hopkins Hospital	110	Radical	22.8
	198	Conservative (mod. Stroganoff)	13.6
Zweifel—Leipzig	394	Radical	18.5
	317	Conservative (venesection)	8.5
Powitzer—Berlin	245	Mixed	18.0
Engelmann—Dortmund	222	Mixed	10.4
Hochenbichler—Vienna	275	Mixed (quartz light)	18.1
Forssner—Stockholm	102	Conservative (Stroganoff)	10.8
Lazard, Irwin, Vruwink and McNeile—Los Angeles	138	Conservative ($MgSO_4$)	13.0
Dorsett and Dieckmann—St. Louis	94	Conservative ($MgSO_4$)	11.7

In this controversy as to the merits of the two methods some writers take very extreme views, for example Liepmann states that the only efficient treatment of eclampsia is by the method of rapid delivery and Stoeckel is similarly inclined. It should be pointed out that any statistics not covering a large series of cases, say at least 100, are of no great value, as in smaller series the numbers are too small to exclude accidental coincidences and consequently the conclusions drawn from them may be entirely misleading. Wilson in 1925 and Williams in 1927 analyzed the eclamptic statistics of this hospital. Williams inclines towards the conservative method of treatment as the result of the analysis of 275 cases treated by both methods. He reports a maternal mortality in the actively or radically treated cases of 22.8 per cent and in the conservatively treated cases of 13.3 per cent.

The Stroganoff treatment is perhaps the most widely used conservative method and the following is Stroganoff's own description of his method:

" 1. Upon admission: (a) Dark room with a minimum of noise. (b) Special nurse. (c) Examination or disturbance of patient only when absolutely necessary, and then usually under chloroform. (d) 0.015 (0.01–0.02) gram morphine hypodermically, while under chloroform narcosis;—usually about 10 to 15 grams of chloroform being employed.

2. One hour after admission: 2.0 (1.5–2.5) grams chloral hydrate per rectum with 100 cc. normal salt solution and 100 cc. milk. Should the patient be conscious the chloral hydrate can be administered without the use of chloroform, except where the patient has had one or more convulsions after admission; then about 10 grams of the anesthetic are used with each dose of chloral hydrate.

3. Three hours after admission: 0.015 (0.01–0.02) gram morphine hypodermically under 10 to 15 grams chloroform.

4. Seven hours after admission: 2.0 (1.5–2.5) grams chloral hydrate, as above.

5. Thirteen hours after admission: 1.5 (1.0–2.0) grams chloral hydrate, as above.

6. Twenty-one hours after admission: 1.5 (1.0–2.0) grams chloral hydrate, as above.

7. After each convulsion: Oxygen is administered as quickly as

possible. This is kept up until the breathing improves, usually about 5 minutes.

8. After three convulsions in the clinic: Venesection of not more than 400 cc. is resorted to.
9. In case of frequent convulsions: Chloroform and chloral hydrate to be used more energetically than outlined above.
10. No convulsions for thirty-four hours: If patient has been free from fits for twenty-four hours or longer after admission, and has not yet been delivered, she should be given about 0.5 grams chloral hydrate every eight hours for about three days.
11. Operative delivery is resorted to only when intervention becomes absolutely necessary for the sake of the child."

Since we know that chloroform produces central necrosis of the liver lobules and that in eclampsia we usually have to deal with a liver lesion, it does not seem logical to employ chloroform in its treatment. Furthermore from studies in this clinic it did not appear to us that venesection was of any great benefit since the fall in blood pressure following it was usually temporary, and in order to dilute the toxins effectively, if such were possible, one would have to withdraw 1500 cc. or more of blood. Consequently, the Stroganoff treatment was modified at the Johns Hopkins Hospital by omitting the venesection, and the following printed directions are at present routinely followed at that institution.

DISPENSARY

"1. Patients must be sent into the hospital whenever they show:
   (a) Systolic pressure of 150 or more and albumin.
   (b) Undue rise in diastolic pressure.
   (c) Any one of the above symptoms associated with severe headache, epigastric pain or pronounced edema.
   (d) Sudden amaurosis, even if none of the conditions mentioned above are present.
2. Patients with increasing blood pressure and definite trace of albumin must visit the dispensary twice a week. If they do not follow directions, Social Service must visit them *promptly*.

WARD SERVICE

Toxemias

1. In moderately sick patients when the albumin does not fall to below 1 gram per liter within a week, or when the general condition is not satisfactory, the induction of labor should be seriously considered.
2. Very ill patients will probably have induction of labor sooner, immediate induction when amaurosis develops suddenly, either with or without pain (epigastric). In primiparae with a rigid cervix, cesarean section may be considered.

Eclampsia

1. *Upon Admission.* Patients with frank eclampsia are:
   (a) To be placed in a quiet darkened room and to be disturbed as little as possible.
   (b) To have special nurse continuously until definitely out of coma.
   (c) To have $\frac{1}{4}$ grain morphia by hypodermic immediately.
   (d) To be catheterized, examined medically and obstetrically and bled for 200 cc. under nitrous oxide anesthesia if conscious. The venesection is done only when it is necessary to obtain a blood specimen for research work.
   (e) To be placed on one side, with foot of bed elevated so long as coma persists. Mucus to be swabbed from pharynx as it collects.
   (f) To have water freely when conscious. If patient cannot drink on account of coma or lack of desire, the intravenous administration of 500 cc. of 5 per cent glucose solution should be considered.
   (g) Not to be delivered until after cervix is fully dilated. Then by the simplest operative means, unless spontaneous delivery seems imminent.
   (h) No chloroform to be used.
   (i) Notify the chemical assistants as soon as patient is admitted, so that the necessary observations can be made.
2. *One hour after admission.* If comatose give 2 grams chloral hydrate in 100 cc. of normal salt solution, and the same quantity of milk per rectum. If conscious the chloral can be administered by mouth in 100 cc. of milk.

3. *Three hours after admission.*
   ¼ grain morphia hypodermically.
4. *Seven hours after admission.*
   2 grams chloral hydrate as above.
5. *Thirteen hours after admission.*
   1.5 grams chloral hydrate as above.
6. *Twenty-one hours after admission.*
   1.5 grams chloral hydrate as above.
   (a) While eclamptic patients are under treatment, the assistants and nurses must insist upon the greatest possible quiet on the fifth floor.
   (b) Catharsis, sweating or venesection in excess of 200 cc. must not be employed.
   (c) No change to be made in above schedule unless authorized by Drs. Williams or Stander."

McPherson, Zubrzycki, King, Speidel, Davidson, Davis, Beck, Bear and Bauch all advocate the conservative method of treatment. Clason in a recent article reports a mortality of 5.6 per cent in a series of 125 cases of eclampsia treated at the General Maternity Hospital in Stockholm by the complete or the modified Stroganoff-Zweifel method, except that pregnancy was interrupted in some of the cases where the symptoms in spite of treatment remained unchanged or became more severe.

Stroganoff himself has reported a large series of cases treated by his method. In his latest communication he states that 578 cases have been treated by his older method and 300 by his improved prophylactic method with a total maternal mortality of about 1 per cent.

From a study of Stroganoff's statistics, Stander found that about 70 per cent of his eclamptic patients had no convulsions before admission to the clinic and developed the condition only after admission; and of these 50 per cent had only one convulsion. He concludes that Stroganoff deals with mild and unneglected cases, while in most obstetrical clinics in this country the patient is usually admitted after having had several convulsions at home and is in a desperate condition. Katsuya, although a believer in the Stroganoff method, objects to the use of morphia, on the ground that it does not affect the cord reflexes, and in its place employs omnopon and scopolamine, which very quickly

inhibit the reflex centers in the cord and exert very litle harmful influence on the center of respiration. Instead of chloral he employs luminal, administered subcutaneously. His maternal mortality for the period of 1922–1925 in the Maternity Hospital at Tokyo was 5 per cent as compared with 20.8 per cent with the original Stroganoff method. Forssner likewise reports a maternal mortality of 8.4 per cent with the conservative treatment of Stroganoff and Zweifel, as against 19 per cent with active treatment.

A great advantage of the conservative over the radical treatment is that it affords us a means to treat intercurrent eclampsia, allow the pregnancy to proceed, and when intervention is necessary it may be done at an elective time. This does not mean that all cases of intercurrent eclampsia will respond favorably to conservative therapy, although it is advisable that this treatment be given a trial before operative procedures are resorted to.

d. Middle line treatment. There are some who believe that better results can be obtained by employing a treatment which is neither conservative nor radical. Zweifel changed from the active method of treatment to the so-called "Mittlere Linie" about 1911 and since that time this method of treatment has been extensively used. The treatment is expectant until it is evident that the conservative method is of no avail and active intervention is then resorted to. Should the patient be a primipara with an undilated cervix Caesarean section may be the procedure of choice, otherwise less radical methods for terminating pregnancy are employed.

From recent work in anesthesia it became apparent that chloroform, ether, nitrous oxide and even ethylene would produce lesions in the liver as well as changes in the concentration of the blood constituents, and furthermore that these changes in the blood constituents very closely simulated those observed in true eclampsia. It was for this reason that Stander suggested that possibly the poor results following active intervention in eclampsia may be explained not by the operative procedure itself but by the general anesthetic usually employed. He therefore recommended, when active intervention becomes necessary in eclampsia, that it be carried out under local or spinal anesthesia. This view is in agreement with the earlier work of Davis and DeLee. It is, furthermore, quite possible that a conservative method of

treatment, followed by operative intervention under spinal or local anesthesia whenever the patient does not improve, will give the best results.

e. Veratrum viride. In order to reduce the high blood pressure which is usually associated with eclampsia, some have used veratrum viride, which produces a rapid fall in blood pressure as well as in the pulse rate. About a half century ago Reamy of Cincinnati introduced the drug in the treatment of this disease. Stevens advocates the injection of 1 cc. as soon as the patient is seen, but considers it dangerous except in the presence of actual convulsions and high blood pressure. He reports a series of 25 personal cases with a maternal mortality of 16 per cent. Haultain and Bourne are both believers in the use of veratrum viride to control the blood pressure in eclampsia, and the latter advocates graduating the dose according to the height of the blood pressure, giving 1 cc. when the pressure is 190 mm. or above, and 0.25 cc. when it is between 140 and 155 mm. He states that after a large dose of veratrum viride the blood pressure may fall as much as 100 mm. Haultain also administers the drug repeatedly in doses ranging from 0.25 to 1 cc., and Smith and Rundlett likewise recommend it.

After the appearance of Cragin's enthusiastic report Williams for a time treated every other case of eclampsia with veratrum viride and the alternate case by the usual method, and found that the results in each series were practically identical. Consequently, the most he could say for it was that it did no great harm, and that it occasionally produced an alarming fall in pressure. It is doubtful whether such a fall in pressure is really beneficial and it should always be borne in mind that a high blood pressure may even be a protective mechanism. A generation ago veratrum was employed with a free hand in the treatment of eclampsia in this country, but at present its use has fallen into desuetude.

f. Venesection. Venesection has been one of the recognized methods of treatment for hundreds of years, and when the "toxic" origin of eclampsia was first advanced, blood letting was justified upon the supposition that it might serve to dilute or reduce the amount of "toxin" in the circulating blood stream. Some also advocate it as a means of reducing the blood pressure. Since phlebotomy was one of the earliest methods of treatment for many diseases, it was quite natural

that it should have been used to combat eclampsia. The amount of blood withdrawn varied from a few hundred cc. to 1000 cc. or 1500 cc., depending upon the severity of the attack and upon the boldness of the physician. Waldstein writes that if diet does not prevent oliguria, headache and ocular symptoms in a pre-eclamptic condition, venesection should be carried out, and in the definitely eclamptic patient he recommends the withdrawal of from 1000 to 1500 cc. of blood, following the venesection by the infusion of sodium chloride. He reports 117 cases of eclampsia so treated with a maternal mortality of 1.7. Eberhard recommends venesection of 500 cc., and Nevermann, Schlossmann, Zweifel, Lichenstein and Moran are among its advocates. Nevermann observed the blood stream and the capillary vessels during the bleeding and came to the conclusion that any improvement following it was due to a mechanical effect—namely the removal of venous blood containing toxins, which resulted in an increased blood flow throughout the circulatory system. Schlossmann also believes that the action of venesection in eclampsia is a detoxicating one, and that any reflex effect or lessening of the viscosity of the blood is secondary. He regards the fall in blood pressure following the bleeding as a measure of the effectiveness of venesection.

The use of venesection in eclampsia has been temporarily discarded in this clinic and Stander writes:

"I cannot help but think that the high blood pressure in eclampsia in many instances may represent a protective mechanism. Consequently, if a change in the semipermeability of the walls of the peripheral vessels plays a rôle in eclampsia, as I believe from experimental data which we are about to publish, it is safe to assume that the early and constant rise of the diastolic blood pressure is due to an increase in the peripheral resistance. If this state of affairs holds true, then a rise in blood pressure should facilitate osmosis and elimination. Additional evidence in support of such a view is afforded by the fact that there is such divergence of opinion as to the value of venesection in eclampsia, as well as by the fact that one often notices a remarkably sudden return of the blood pressure to its original high level after a venesection. Moreover, I cannot agree with Stroganoff in thinking that a venesection of 200 to 300 cc. can be of any material value in lowering the blood pressure or in the elimination of "toxins," and I hold that either it should not be employed at all, or if it is, that large quantities should be withdrawn (750–1000 cc.)."

g. Ammonium chloride. In order to treat the oedema which is often an accompaniment of eclampsia, Mussey suggested the use of ammonium chloride. He states that its use is generally followed by prompt diuresis, disappearance of oedema, marked loss of weight, lowered blood pressure and improvement of the patient, and that the improvement is usually greater and more lasting than that obtained by dietary methods. He also believes that the increased excretion of urine and the decrease in the oedema, with resulting loss of weight following its use, probably carries off from the tissues a sufficient amount of toxin to improve the condition. He warns that, although there is usually little or no increase in the blood urea in eclampsia, ammonium chloride should not be used without previous determinaton of the blood urea content and the alkali reserve, as these may become markedly increased following the use of the drug.

Iverson and Nakazawa believe that oedema is usually caused by a low colloid osmotic pressure. They found that in four cases with acute albuminuria there was a decrease in the colloid osmotic pressure sufficient to account for the oedema. They called attention to the fact, however, that increased hydrostatic pressure due to impaired circulation may also be an important factor.

h. Squatting posture. Lichenstein, believing that insufficiently oxidized protein substances may develop in a retro-placental hematoma and cause eclampsia by their absorption, claims that the best results in its treatment may be obtained by having the patient assume a squatting posture. He states that, as the intra-abdominal pressure is about three times as great in the squatting as in the recumbent posture, the former will tend to prevent the formation of a retro-placental hematoma, by making placental separation more difficult. This squatting posture is attained by having the patient's head and shoulders raised and the legs flexed by means of pillow supports. Hammerschlag in discussing the effects of this posture after delivery, states that it is of little value in the treatment of eclampsia.

i. Ultra violet rays treatment. Hochenbichler was the first to investigate the action of the quartz light in patients suffering from the late toxemias of pregnancy. He showed that the rays lower the blood pressure and also decrease any existing acidosis. Kermauner also recommends the use of ultra violet rays and believes that their good

effect may be due to their action on the vessel spasm in the kidneys, brain or skin. The number of cases thus far treated by this method is too small to justify any definite conclusions as to its efficiency; but as its application is simple and apparently harmless, further reports as to its clinical value will be awaited with interest.

j. Kidney decapsulation. The theory that eclampsia is due to failure of the excretory organs to eliminate any accumulating toxins of pregnancy, has led some investigators to remove the capsules of the kidneys in order to facilitate the function of those organs. Edebohls first performed renal decapsulation in a case of eclampsia in 1902, and since that time the subject has been reviewed by many writers, notably Pinard. Lübbert reported two cases where stripping off of the kidney capsule resulted in cessation of convulsions and complete recovery, and Cardwell and Brindeau both recommend it. Jullien reported a case successfully treated by decapsulation, but confesses that the indications for such intervention are very obscure, as some of the severest and most alarming cases often recover spontaneously and quite unexpectedly. He states that in 80 per cent of the cases decapsulation has given a good functional result, although the mortality ranges around 40 per cent. In general, it may be said that decapsulation is very rarely practised today in the treatment of eclampsia.

k. Lumbar puncture. According to the oedema theory of Zangemeister, intra-cranial pressure plays the most important rôle in eclampsia, and it may be relieved in either of two ways—by lumbar puncture or by trephining. Lumbar puncture was used in the treatment of eclampsia in 1904 by Krönig. Voron and Mantalin report three cases so treated after the usual treatment with sedatives and eliminants had failed. In each instance they obtained a clear fluid under normal pressure, and its removal was promptly followed by marked improvement, especially of the nervous symptoms, visual disturbances and headaches.

Wieloch recommends the use of sub-occipital trephining for both diagnostic and therapeutic reasons. He removes as much as 58 cc. of fluid and measures the tension according to the method of Kausch. He states that the pressure in the cisterna is normally about 150 mm. of water and approximately the same as in the lumbar canal. He found an increase in pressure in all his eclamptic cases except one,

which sometimes was as much as 100 mm. He states that in over 50 per cent of the cases the blood pressure falls after the puncture is made, and that diuresis was produced in 38 per cent. He goes so far as to recommend trephining not only in true eclampsia, but in pre-eclamptic patients as well. Years ago lumbar puncture was intermittently practised in this clinic, but the results following it were so little encouraging that its employment was abandoned.

l. Pulmonary oedema. As we all know, eclamptic patients sometimes succumb to pulmonary oedema, and Moore and Lawrence state that pulmonary oedema was the immediate cause of death in about one third of their fatal cases. Because of the high incidence of death due to this complication, these authors developed a method of providing continuous endo-bronchial aspiration, by means of an apparatus which is very simple and readily transportable, and whose employment they state presents no unusual difficulties to one trained in bronchoscopic technique. They advise that a bronchoscopist should be available in every obstetrical service.

Towards this same end Tweedy long ago directed attention to the necessity of preventing oedema of the lungs, by placing the patient in such a position that the nose and mouth are lower than the bottom of the chest, and turning her from side to side every half hour. To prevent aspiration of saliva into the bronchi and to retard the development of pulmonary oedema, it is customary in many clinics to have the foot of the bed elevated about 10 inches off the ground and to have the patient lie on her side with special instructions to the nurse to swab out the patient's throat whenever necessary.

m. Serum. Mayer in 1913 reported a case in which the serum of a normal pregnant woman was used to treat the eclamptic condition and was followed by recovery. A lumbar puncture was done and 5 cc. of fluid extracted, and this was replaced by the injection of 5 cc. of normal blood serum from a healthy pregnant woman. Recently McMahon recommended the use of blood serum obtained from eclamptic patients. This is given intravenously in doses ranging from 40 to 160 cc. He reports ten patients treated successfully by this method.

In the Boston Lying-In Hospital there has been developed a new serum method, which puts into practice the method of plasma-phaeresis which was developed experimentally by Abel some years ago.

Dr. Irving in a personal communication described this method as follows,

"To begin with it is not a serum treatment at all but a removal of a certain amount of the blood plasma; in other words a plasmaphaeresis done much as Abel, Rowntree and Turner did theirs on dogs. We proceed as follows. When an eclamptic is admitted she is at once started on the Stroganoff regime. She is then bled 1 liter into citrated solution under sterile precautions. The blood is then decanted into four sterile centrifuge flasks of 500 cc. each. Each flask contains about 250 cc. of citrated blood. The two flasks which are to be opposite each other in the centrifuge are balanced on the scales, using the necessary amount of salt solution for the purpose. The flasks are then covered with sterile paper caps and the whole number of them centrifuged for twenty minutes. They are then removed from the machine and the supernatant plasma pipetted off. We do this by using a sterile siphon tube which goes through one of the holes ina two hole stopper into a flask. Through the other hole goes a suction tube to start the siphon.

Enough normal saline to make the total amount in each flask up to about 250 cc. is now added. The corpuscles are now diffused in the salt solution by gently rotating the flasks. The flasks are balanced as before, centrifuged again for twenty minutes, and the supernatant salt solution siphoned off. In other words, we wash the corpuscles once. We then make the total quantity up to about 1 liter with normal saline and reinfuse it into the patient.

We do not feel that this is the only way to treat eclampsia. We do think, however, that it enables us to do venesections of large extent and leave our patients no worse for them. In most cases we find that the red count is no less after the plasmaphaeresis than it was before. If toxemia is caused by a toxin in the circulation it is probably in the plasma and not in the corpuscles. By removing a considerable portion of the plasma we feel that we are carrying out a rational procedure.

We have done this about fifteen times, and on two patients, twice. We have had only four eclamptics, all of whom recovered. We have also been able to reduce the blood pressure in preeclamptic toxemia, where, following delivery, there had been no reduction of the hypertension. It has done no good to the chronic nephritics. Our chief difficulty has been in getting enough eclamptics to use the method on."

n. Liver extract. Miller and Martinez have used liver extract or "heparmone" in the treatment of eclampsia. They write:

"If perchance the liver has a certain neutralizing function, which could be conserved by the addition of liver substance, however given, it would make little or no difference regarding the nature or source of the toxic agent of eclampsia provided the vital capacity of the liver could be increased at will to meet the emergencies of the situation. With this thought as a background we began (October 1926) the use of heparmone in the treatment of pre-eclamptic and eclamptic cases."

In their latest communication these authors report 43 consecutive eclamptic cases so treated, with a maternal mortality of 6.9 per cent. If they can continue to obtain such excellent results in a large series of cases the use of heparmone in the treatment of eclampsia will be certainly warranted. They report no untoward symptoms or results following the use of the extract, although in some women they gave as much as 275 cc. intravenously within a period of 12 hours. Their results are a stimulation to a further experimental and clinical test of the efficacy of this extract.

o. Magnesium sulphate. The intravenous administration of magnesium sulphate has been fairly extensively used in the treatment of eclampsia during the past ten years, and some authors, such as Lazard, Rucker, and Dieckmann, report excellent results.

Stander, in a recent review of the results obtained with this drug, concluded that the clinical experiences, as reported in the literature, are encouraging, but warned against the intravenous administration of too large a dose or too concentrated a solution of the salt. He advocated that when the drug be given intravenously, the strength of the solution should not exceed 10 per cent, and that at no time should the patient be given more than 20 cc. of such a solution, as in dogs he was able to produce liver lesions, and in some cases death, by the intravenous administration of too large an amount, or too concentrated a solution, of the sulphate. He considers that a total of 6 grams of $MgSO_4$, administered intravenously in 20 cc. doses of a 10 per cent solution over a period of about twenty-four hours, is within the limit of safety for an average-size woman, but that anything exceeding this may prove dangerous. The intramuscular administration of magnesium sulphate may be a safer procedure.

Lazard and his co-workers have treated a large series of eclamptics with this drug, with fairly good results, and are enthusiastic advocates

of its use. As further reports are published on the therapeutic value and toxicity of magnesium sulphate, we may be able to arrive at a truer evaluation of its worth in the treatment of eclampsia.

p. Diet. A great deal has been written about diet in eclampsia, and our attention was definitely focused on the amount and type of food the eclamptic patient received, when we learned that a marked reduction in the incidence of eclampsia had occurred during the war, at a time when the women were receiving less food than normally and when the diet consisted mainly of carbohydrates. Tweedy and his coworkers believe that the diet may even function as an etiological agent in the production of eclampsia, and consequently lay particular stress on the kind and amount of food patients should receive. Persson states that the treatment of eclampsia is one of diet and in the more severe cases venesection may be of help. Mastre recommends a diet low in protein and salt. Diet is undoubtedly of help in the prophylactic treatment or in the pre-eclamptic, but the average eclamptic patient that one sees in the hospital or at home, and who has had three or four or more convulsions, is usually semi-conscious and unable to take any food or fluids, even should it be desirable.

The Dublin School of obstetricians, under the leadership of Tweedy and others, have developed a particular method of treating eclampsia which has especially aroused our interest because Eden, in his careful report to the British Congress of Obstetricians and Gynecologists in 1922, showed that the maternal mortality following the use of the Dublin method was the lowest in the British Isles. According to Solomons, the method consists primarily in starvation, gastric lavage, bowel lavage, morphia, injection of sodium bicarbonate under the breast and close observation to prevent drowning or other accidents. In most cases the patient receives nothing but water for several days and should there be no improvement Caesarean section may be performed. The gastric lavage is continued until the water returns clear, when 2 oz. of magnesium sulphate solution are left in the stomach. The bowel lavage is given with the patient on her left side, with the tube inserted 18 inches into the bowel. Sodium bicarbonate, 1 gram to one pint, is used until the bowels are clear and then one pint of the solution is left in the bowel. Solomons writes that recently they have omitted the use of morphia and states that their average maternal mortality is about 10%.

q. Morphia. Morphia has been used for half a century in the treatment of eclampsia. Gustav Veit was the first to propose its routine use, and since his time this drug has been employed either alone or in conjunction with other methods of treatment. Stroganoff developed his method of treatment with morphia as its basis. Roe reported a series of thirty-two cases treated by morphia and colonic irrigation. This author uses 0.02 gram of the drug upon admission to the hospital, with half this dose again in another half hour, continuing with 0.001 gram at hourly intervals thereafter. Rouvier treats his cases in a similar way using small doses of morphia repeatedly at frequent intervals, and is enthusiastic as to its effect. Ferrere states that the maxi mum beneficial dose of morphia in the treatment of eclampsia is 0.12 gram but that larger doses may be given without danger to the patient. McPherson, at the New York Lying-In Hospital, has reported large series of cases treated with this drug. He gave morphia till the respirations fell to 8 per minute. In this clinic, some years ago, we did likewise, but at present never administer more than $\frac{1}{4}$ grain at one time nor more than $\frac{3}{4}$ grain in twenty-four hours.

It has recently been shown that morphia raises the CO_2 combining power of the blood, and this property, together with its sedative action, may explain the good results following its use in eclampsia.

r. Acidosis treatment. One of the most characteristic features in most cases of eclampsia is a marked acidosis, as has already been discussed above. The CO_2 combining power in the average case ranges around 30 volumes per cent, and in severely ill patients it is not unusual to see it drop as low as 15 volumes per cent. Following the work of Thalhimer on the use of insulin in post-operative acidosis, Stander and Duncan tried insulin to combat the acidosis of eclampsia. They followed the suggestion of Thalhimer and gave a protective dose of glucose, amounting to 2 grams of glucose per unit of insulin, in order to prevent the development of hypoglycemic symptoms. Insulin alone, as well as insulin together with glucose, has been quite extensively used during the past few years to overcome the acidosis in severe eclampsia. In general it may be said that when the CO_2 combining power drops below 30 volumes per cent, the patient is suffering from an acidosis which is probably the result of the eclampsia, and when it falls below 20 volumes per cent, the patient is usually desperately ill and is in urgent need of anti-acidosis treatment.

Collazo and Dobreff tested the action of insulin on the glands of external secretion and came to the conclusion that it definitely affects the basal metabolism, water distribution, colloidal condition of the cells, and such ferments as diastase.

Loeser reports 45 cases treated successfully with insulin and recommends that in eclampsia 20 to 40 units of insulin, together with 1 to 2 grams of glucose per unit of insulin be given. Vogt regards insulin and glucose as an excellent treatment for eclampsia. He administers from 5 to 50 units daily, combined with an enema of from one half to 1 liter of a 3 to a 5 per cent solution of dextrose. The acidosis of eclampsia may also be combated by drugs other than insulin. Wilson in a recent article recommends the use of sodium bicarbonate and places special emphasis on the CO_2 combining power as an index of the degree of acidosis. This author feels that while glucose will distinctly relieve an alkali deficit in either eclampsia or vomiting of pregnancy, it cannot be relied upon to raise the CO_2 combining power of the blood speedily enough in urgently sick patients. He regulates the dose of sodium bicarbonate to avoid producing an alkalosis, and combines the sodium salt with glucose injections wherever feasible.

Rodenacker believes that eclampsia is the result of a disturbance of oxidation and therefore recommends the use of insulin as a preventive in all cases where the oxidation is known to be disturbed. Schwab recommends the use of oxygen in severe cases of eclampsia because he believes that the intoxication from CO_2 is one of the principal dangers in eclampsia.

s. Summary. From this review of the various methods of treatment, it must be apparent that we have as yet no satisfactory way of combating this dreaded disease, whose average maternal mortality of 10 to 20 per cent is still far too high, while the foetal mortality, approximately 30 per cent, is much worse. We do not know the cause of the disease, and our treatment is consequently entirely empiric or symptomatic. At present the most logical and most promising treatment appears, to the author, to be one which is conservative, associated with radical interference under spinal or local anesthesia, should the conservative methods prove of no avail and the patient's condition become progressively worse.

Frequent blood analyses will reveal the presence or absence of a developing acidosis, and should the CO_2 combining power of the blood

fall to dangerously low levels (25 volumes per cent or lower) anti-acidosis treatment is urgently needed. For such a purpose, insulin with a protective dose of glucose, usually 30 units insulin and 60 grams of glucose in a 10 per cent solution, often acts efficiently.

In order to compare the different methods of treatment as practised in various lying-in hospitals, the author communicated with many of the leading obstetricians in this country and abroad. They were asked to state their views regarding the etiology, method of treatment and results obtained in eclampsia. The information gathered in this manner was most interesting and instructive. It was the general opinion that the cause of the disease is as yet unknown, and that it will probably be discovered in the course of metabolic investigations. The following table represents in brief the types of treatment employed.

CLINIC	TREATMENT
Bailey, New York	Conservative
Brindeau, Paris	Radical
Caldwell, New York	Conservative plus paraldehyde
Danforth, Evanston	Conservative plus venesection
Davis, Milwaukee	Conservative plus magnesium sulphate
DeLee, Chicago	Radical
Dieckmann, St. Louis	Conservative plus magnesium sulphate
Duncan, Montreal	Conservative
Ehrenfest, St. Louis	Conservative and occasional section
Foulkrod, Philadelphia	Conservative plus induction (rupture membrane)
Holmes, Chicago	Conservative
Johnstone, Edinburgh	Conservative plus colonic lavage
Keller, Philadelphia	Autogenous vaccines and middle line therapy
Lazard, Los Angeles	Conservative plus magnesium sulphate
Litzenberg, Minneapolis	Conservative plus venesection
Miller, New Orleans	Conservative
Miller, Pittsburgh	Conservative plus heparmone
Mussey, Rochester, Minn	Conservative
Newell, Boston	Conservative
Piper, Philadelphia	Middle line therapy
Plass, Iowa City	Conservative
Polak, Brooklyn	Conservative plus magnesium sulphate
Rucker, Richmond	Conservative plus magnesium sulphate
Schumann, Philadelphia	Conservative and occasional section
Solomons, Dublin	Conservative plus gastric and colonic lavage
Spalding, San Francisco	Conservative
Titus, Pittsburgh	Conservative plus glucose
Ward, New York	Conservative plus bag induction
Wilson, Rochester, N. Y.	Conservative

From this it will be seen that conservative treatment has in great part replaced operative interference in the treatment of the disease. It is also interesting to note that many authors are swinging toward a "middle line" therapy and are advocating Caesarean section under local or spinal anesthesia in certain selected cases.

Eclampsia in mother and child. Cases have been reported of eclamptic convulsions in both mother and child. Schwarzkoph in 1927 described 30 cases collected from the literature and Loebel, Kissinger and Laffont, and Gaujoux also report similar cases. It goes without saying that such cases are of great practical and scientific interest, as they indicate that the disease is due to the circulation of some "toxic" substance. At the same time great caution should be used in accepting them unless both mother and child have been subjected to autopsy and the existence of the characteristic liver lesions have been demonstrated in both by competent histological examination.

The mortality of children of eclamptic mothers is about 40%, according to Neugarten. He studied the fate of 81 living children of eclamptic mothers and found that after one year or more six of them had died, although the causes of death had no direct relationship to the maternal eclampsia. Of the 81 living children, 24 were re-examined in the hospital, one had suffered from convulsions, and all were entirely normal in physical and mental development.

In a recent contribution, Tunis analyzed the foetal mortality as recorded from different clinics in Germany, and prepared the following table.

Foetal mortality in eclampsia

	per cent
Zweifel	37
v. Franque	41
Lichtenstein	39
Zacheral	35
Weingarten	35
Bund	30
E. Martin	10
R. Freund	11.5
Heinlein	16
Stoeckel	8.6

He further compared the foetal mortality in Waldstein's Clinic with that of Esch, and found the former to be 10.8 per cent and the latter

40.2 per cent. He explains this marked difference by the fact that Waldstein employs active therapy while Esch adheres to the conservative treatment.

It will be seen that the foetal mortality is on the average about 30 per cent, and although our first consideration in the treatment of eclampsia is the welfare of the mother, it is hoped that the future may teach us to reduce further this appalling foetal mortality.

VI. Acute yellow atrophy of the liver

Acute yellow atrophy of the liver, also known as icterus gravis, is an acute necrosis of the liver cells accompanied by jaundice, disturbances of cerebration, and reduction in the size of the liver. According to Thierfelder and Quincke, about 60 per cent of all cases reported in the literature had occurred in pregnant women. The disease usually proves fatal, but, fortunately, is of very rare occurrence, as only a few hundred cases have been reported.

Etiology. The cause of the disease is unknown. Williams states that poisons, such as chloroform, arsenic, mercury and phosphorus, as well as certain diseases (syphilis, septicemia and congestion and cirrhosis of the liver) may be predisposing factors in some of the cases reported. Titus suggested that acute yellow atrophy of the liver may have the same etiology as eclampsia and vomiting of pregnancy. Certainly nothing definite is known regarding the etiology of the disease.

Pathology. The outstanding finding in acute yellow atrophy of the liver is the remarkable hepatic atrophy. The liver is often reduced to less than half its normal size, with a corresponding decrease in its weight, and a softening in its consistency. Central necrosis of the liver lobule is the characteristic histological picture, although the necrosis may extend throughout the lobule in the severe type of the disease. The interlobular spaces are not affected, the blood vessels and bile canals maintaining a normal appearance; associated with the hepatic lesions, one often finds acute changes in the epithelial lining of the convoluted tubules of the kidney, while the collecting tubules and glomeruli remain normal.

Symptoms. The disease may develop very suddenly, with sharp abdominal pain, headache and vomiting. Delirium, coma or con-

vulsions may follow quite promptly these prodromal symptoms. Jaundice develops rapidly and may become quite marked. The pulse and respiration are rapid; while, in contrast to the usual picture in eclampsia, the blood pressure is not elevated and the urine contains a slight amount of albumin. Instead of this rapidly developing course, the onset of the disease may be less acute and simulate pre-eclampsia. For a detailed description of the symptoms the reader is referred to the standard text-books on Obstetrics.

In the differential diagnosis between acute yellow atrophy of the liver and vomiting of pregnancy or eclampsia, the clinical course, and particularly the presence of icterus, the size of the liver, examination of the urine for leucine, tyrosine and the nitrogen partition, as well as analysis of the blood will be of definite assistance. We have already noted the changes in the urine and blood which usually accompany vomiting of pregnancy and eclampsia, respectively. It should also be noted that a general septicemia due to the gas bacillus may sometimes simulate acute yellow atrophy; and it is often very difficult to differentiate clinically between these two conditions. This was exemplified by a patient observed in this clinic last year, and Kohl in 1928 directed attention to the jaundice, cyanosis and the hematuria,which may occur in the former condition.

Stadie and van Slyke reported increased amino-acid nitrogen in the blood of a patient suffering from acute yellow atrophy of the liver. Wells studied the chemical composition of the liver in a case of acute yellow atrophy and found a considerable number of amino-acids, some of which had not previously been found free in human tissues. These amino-acids were leucin, tyrosin, glycocoll, alanin, pyrrolidin-carbonic acid, glutaminic acid, aspartic acid and lysin. Though histidin was also present, he was unable to isolate it. He obtained a total of 8 grams of amino-acids from approximately 700 grams of liver tissue, corresponding to about 12 grams of amino-acids in the entire liver. He agrees with Neuberg and Richter that all the amino-acids present could not have been derived from the autolyzed liver cells. There was also present a decrease in the diamino nitrogen. Sulphur was normal, while phosphorus was increased and the amount of fat, both free and combined, was below normal.

Oastler and Jacobi studied a case of acute yellow atrophy of the liver

and found that the blood had an increased urea content amounting to 50 mgm. The uric acid in the blood was 3.3 mgm. and the creatin about 2 mgm., while the CO_2 combining power of the blood was 40 volumes per cent. The patient's urine revealed the presence of leusin and tyrosin.

Treatment. Liver injury appears to be the outstanding characteristic of this disease, and from the experimental work of Whipple, Mann and others on hepatic damage, it would seem that the best therapy would be the administration of glucose. The glucose may be given intravenously in 10 per cent solution. The disease usually ends fatally, although Wilson and Goodpasture are more optimistic and state that recovery from acute yellow atrophy of the liver is probably more frequent than is generally believed.

The author wishes to express his sincere thanks to the many obstetricians, whose names unfortunately cannot be mentioned here, who were kind enough to furnish him with information regarding their views, laboratory findings and clinical results. He feels especially indebted to Dr. J. Whitridge Williams for many valuable suggestions.

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INDEX

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